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Genome

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IT'S HOW ONE WOMAN FIGHTS LUNG CANCER.

IT'S HELPING DOCTORS BETTER ANALYZE YOUR DATA.

IT'S REVOLUTIONIZING PRENATAL TESTING.

WHAT IS PERSONALIZED MEDICINE?

IT'S STUDYING TRILLIONS OF MICROBES IN YOUR GUT.

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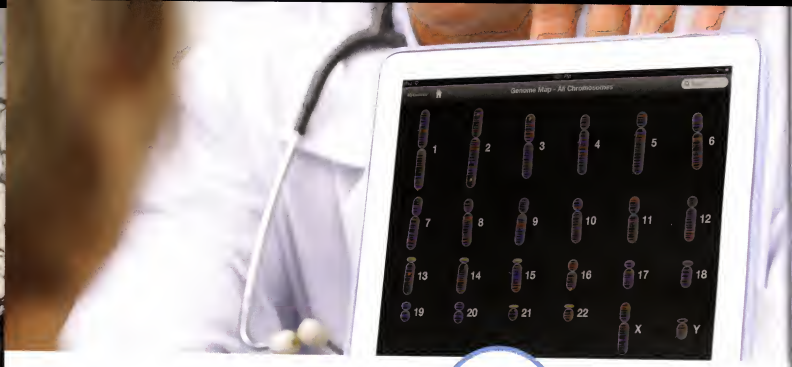

It starts with you

And others like you, who think big about genomics and healthcare.

Turning precision medicine into the standard of care requires a large group of stakeholders working together to mobilize and tackle the barriers. The technology is here, but progress is needed in areas such as genomic education, regulations, reimbursement, and data interpretation.

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To learn more about *Understand Your Genome*, visit www.illumina.com/UYG

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FEATURES

"THE PROBLEM WITH THESE TEST KITS IS SCIENTIFIC. ONLY PART OF A PERSON'S DNA IS TESTED, AND SCIENTISTS ARE STILL UNSURE HOW TO INTERPRET MOST OF THE INFORMATION."

ON THE COVER
Photograph by Adam Voorhes

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"IT WON'T BE LONG BEFORE FETAL CELL-FREE DNA TESTING BECOMES STANDARD OF CARE FOR ALL WOMEN."

ONLINE

TO FOLLOW ON TWITTER

Geoffrey Ginsburg, MD, PhD
@PersonalizedMed
The personalized medicine pioneer (and *Genome* editor-at-large) tweets links about the latest advances in genomic medicine.

Carl Zimmer
@carlzimmer
The *New York Times* columnist is a science writer and blogger.

Eric Topol, MD
@EricTopol
The trailblazing editor-in-chief of Medscape stays on top of the fast-changing digital medicine industry.

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DEPARTMENTS

Genome

YOUR HEALTH IS PERSONAL | SPRING 2014

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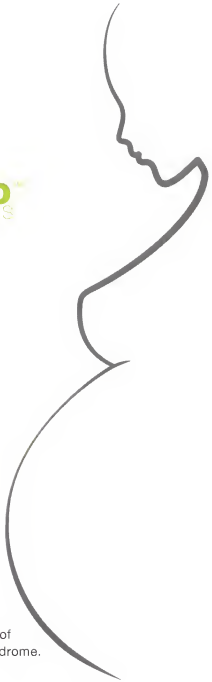

The microdeletions that Panorama screens for:

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- **The Importance of Microdeletions** *with Dr. Ronald Wapner*
- **Panorama NIPT Goes Micro** *with Dr. Susan Gross*

This is a revolutionary time in prenatal medicine. Only recently have geneticists discovered the prevalence of microdeletions in pregnancies that were otherwise considered low risk. Now scientists from Natera have developed the ability to screen non-invasively for a subset of these conditions, including 22q11.2 deletion/DiGeorge syndrome.

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The tests were developed by Natera, Inc., a laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA). These tests have not been cleared or approved by the U.S. Food and Drug Administration (FDA).

A Bug's Life

This scanning electron micrograph shows just a few of the tiny microbes that live on or in each of us — and these microscopic bugs could hold the keys to your health.
See story on page 40.

PHOTOGRAPH BY MARTIN OEGGERLI

By Jeanette McCarthy, MPH, PhD

Welcome to the Future of Medicine

A greater understanding of our DNA is revolutionizing healthcare. Genome *explores how this personalized approach to treatment affects you.*

In 2001, while working at startup biotechnology company Millennium Pharmaceuticals, my colleague Geoffrey Ginsburg and I wrote an opinion piece in *Nature Biotechnology* about the new field of personalized medicine. After the first draft of the human genome sequence (which would be completed in 2003), it was evident that this newfound knowledge of human genomics had the potential to dramatically alter how medicine was practiced. We and others were hopeful that medicine would move away from the trial-and-error, one-size-fits-all approach to diagnosis and move toward classification of disease according to the patient's molecular profile, leading to treatment tailored to the individual.

Last year in *Science Translational Medicine*, we recounted the various successes of the past decade of personalized medicine and outlined the myriad challenges that still face the field. While we celebrated the use of genomics in targeting cancer treatments, solving diagnostic dilemmas, and improving prenatal diagnosis, our enthusiasm was tempered by low uptake of these technologies outside of academic medical centers. Further examination uncovered a healthcare system that was not primed to incorporate these advances, neither from a technical/logistical standpoint nor from an intellectual one. It was becoming increasingly clear that this field was going nowhere without knowledgeable healthcare providers, patients, and other stakeholders. That's when I turned in my lab coat and began in earnest to focus on personalized medicine education.

> "OUR GOAL IS SIMPLE: TO TRANSFORM THE WAY HEALTHCARE IS DELIVERED BY INSPIRING PEOPLE TO DEMAND THE CARE THEY DESERVE."

Surveys of physicians indicate a general lack of awareness of available genomic tests, the skills to use these tests, and an appreciation of the associated ethical, social, and economic issues. Today's physicians don't have time to retrain themselves in genomics. Many genomic tests lack the evidentiary framework to substantiate their clinical validity and utility. Current information on genomic tests is diffuse, and there are limited unbiased third-party sources of information to turn to. At the same time, patients, whose health is at stake and who have the most to gain from personalized medicine, are connecting with each other via social networks, embracing technologies

ILLUSTRATION BY MELINDA JOSIE

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Editor's Note

for monitoring their health, and seeking health information on their own. These patients represent the exact kind of disruptive force needed to propel personalized medicine forward.

Lee Hood, a pioneer in the genome sciences, coined the term "P4 medicine" to capture the growing importance of the patient's voice in medicine — the notion that personalized medicine should not only be predictive and preventive, but also *participatory*. Educated and engaged patients can and will play a major role in advancing personalized medicine, but they need trusted sources of information. That's why we created *Genome* magazine and why I was so excited to join as editor-in-chief. Our goal is simple: to transform the way healthcare is delivered by inspiring people to demand the care they deserve. Our vision: a world in which everyone knows the power of his genome.

The *Genome* team has been busy the past few months. We've assembled a world-class scientific advisory board, laid out story ideas for upcoming issues, and launched our website. Our advisory board consists of thought leaders in the field of personalized medicine who are on the ground, pushing the field forward. Their role: to make sure that the conversations going on among doctors and researchers about personalized medicine are mirrored in *Genome* and that our stories are scientifically sound. What kinds of stories will you read in *Genome*? You'll read about available genomic tests and treatment options across a range of common diseases, including heart disease, cancer, diabetes, and others. The first issue takes a deep dive into breast cancer but also covers more general areas like prenatal testing and genome sequencing of healthy individuals. You'll get a glimpse of research innovations that will impact medicine in the future, such as the study of your microbiome, the trillions of microorganisms that colonize your body. You'll learn about legal, social, and economic issues facing genomic medicine, like the FDA crackdown on direct-to-consumer genetic testing company 23andMe. You will hear firsthand patient stories about experiences with personalized medicine and learn from the experts.

> "EDUCATED AND ENGAGED PATIENTS CAN AND WILL PLAY A MAJOR ROLE IN ADVANCING PERSONALIZED MEDICINE."

Between issues of our quarterly print magazine, you can visit us at our website (genomemag.com) to read weekly updates on personalized medicine news that affects you, to find resources and links to additional information, and to let us know what you want to read about.

Genome will be *the* source for practical, actionable information about health and healthcare for patients, caregivers, and healthcare providers. By telling engaging stories about new tests and treatments and other aspects of personalized medicine, we hope to enable patients to live longer and better lives. Welcome to the future of medicine. We hope you enjoy *Genome*!

Jeanette McCarthy is the editor-in-chief of *Genome*, an adjunct associate professor of community and family medicine at Duke University, and a visiting associate professor of medicine at the University of California San Francisco, Division of Medical Genetics.


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Live in Nigeria
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By Carl Zimmer

Record Collection

Doctors want to merge health information with genomic data to better understand disease. But at what cost to privacy?

Medical research is entering the age of Big Data. Health records — doctors' notes, diagnoses, prescriptions, blood pressure readings, etc. — are now gradually being digitized. Scientists are developing programs that can intelligently search the records of thousands of patients for significant patterns, such as risk factors for various diseases.

Another source of medical Big Data is lurking in our own cells: the human genome. The cost of sequencing a person's genome has dropped to a thousand dollars and will continue to plummet. More and more volunteers are agreeing to have information about their DNA stored in online databases, making it possible for scientists to scan their genes for clues to maladies ranging from heart disease to schizophrenia.

The dream of many medical researchers is to merge these two kinds of Big Data: to be able to investigate a single database housing the medical records and genetic information for thousands of people.

A number of projects are underway to combine these two forms of Big Data. In Britain, for example, half a million people have volunteered to be a part of UK Biobank. In the United States, the National Institutes of Health has organized several medical centers with electronic health records into the Electronic Medical Records and Genomics (eMERGE) Network. Researchers who have analyzed the eMERGE data from 13,000 people have already discovered a number of new links between gene variants and diseases ranging from skin cancer to anemia.

> “MAKING INFORMATION ANONYMOUS IS HARDER THAN IT SEEMS WHEN THAT INFORMATION IS MEDICAL.”

But medical Big Data is different in one important way from Big Data for linguistics or archaeology or most other sciences: the matter of privacy. It's hard to imagine anything more private than your health records or your genome. The prospect of having huge databases with both kinds of information linked in one place makes identity theft seem unobtrusive.

The prospect of poached health data has raised worries that people could lose their insurance or face discrimination for jobs. Already, safeguards such as the Genetic Information Nondiscrimination Act (or GINA, which protects against discrimination in health coverage and employment) have been put in place.

To ensure the privacy

ILLUSTRATION BY MELINDA JOSIE

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You'll find these and other stories in upcoming issues:

Groundbreaking research into Alzheimer's disease treatment | How personalized medicine is changing the way we conduct clinical trials | What diseases run in your family and why that matters | Reimbursement issues for genomic tests and targeted treatments | The science and ethics behind the idea of "designer babies" | The fascinating new world of personalized dentistry

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of their databases, Bradley Malin and his colleagues at Vanderbilt have spent years creating new safeguards. Vanderbilt's Medical Center has been digitizing medical records since the early 1980s. To turn these records into a research database, Malin and his colleagues gave each patient a number. In 2007, Vanderbilt began stocking a bank of blood samples taken from the blood left over from tests. With the consent of patients, the researchers assigned the same numbers to the blood samples — and to the DNA sequences they later obtained from them. Once the medical records and DNA go into the research database, they no longer have a formal link to the patient.

Making information anonymous is harder than it seems when that information is medical. Clues about people's identities can slip through in all sorts of forms. Vanderbilt's research database of electronic health records contains every piece of information that the university's medical system accrues about each person: X-rays, billable diagnostic codes, discharge forms, and so on. A doctor's hand-scribbled notes may include a stray reference to a patient's name. Even the dates on medical records could allow someone to discern a patient's identity.

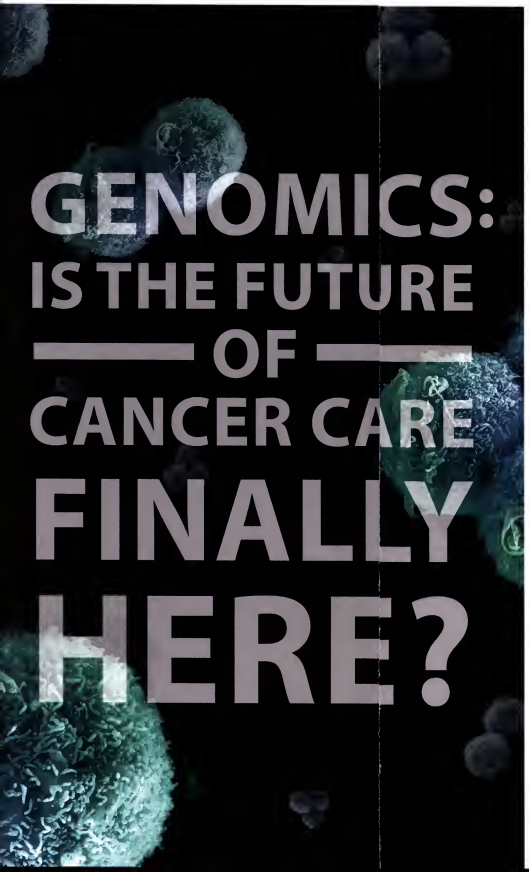
> “MASSIVE DATABASES OF MEDICAL AND GENETIC INFORMATION COULD HELP US UNDERSTAND HUMAN BIOLOGY FAR BETTER THAN WE DO TODAY.”

To combat this, Malin's group redacted patient names from the medical records. They also changed and randomized the dates on every record. Scrambling the dates sacrificed some types of research. If a flu expert wanted to see how the Vanderbilt patient population fared during a flu season, the database would be useless. But researchers can still, for example, see how people with a certain gene variant react to a particular arthritis drug.

The scientists aren't just protecting the privacy of their patients from an unscrupulous scientist or a hacker. There's also the risk that government officials might demand to use the database to get information on an individual. So Malin and his team randomly drop a fraction of the patients from the database, with no way of knowing who's in and who's out. The government would have to analyze all the millions of records in order to find clues to one individual.

Such safeguards are important. Massive databases of medical and genetic information could help us understand human biology far better than we do today. Although everyone can benefit from those insights, scientists will need to ensure that everyone can't probe our medical secrets along the way.

Carl Zimmer is a columnist for the *New York Times* and the author of a dozen books about biology. For more information, visit carlzimmer.com.



Lung cancer cells as seen in an electron micrographic scan.

GENOMICS: IS THE FUTURE OF CANCER CARE FINALLY HERE?

Advanced genomic testing. Have you heard of it? Not everyone has, but in the fight against cancer it's an exciting development. It's more than a promise for the future. It's giving hope to many cancer patients today.

Cancer Treatment Centers of America®
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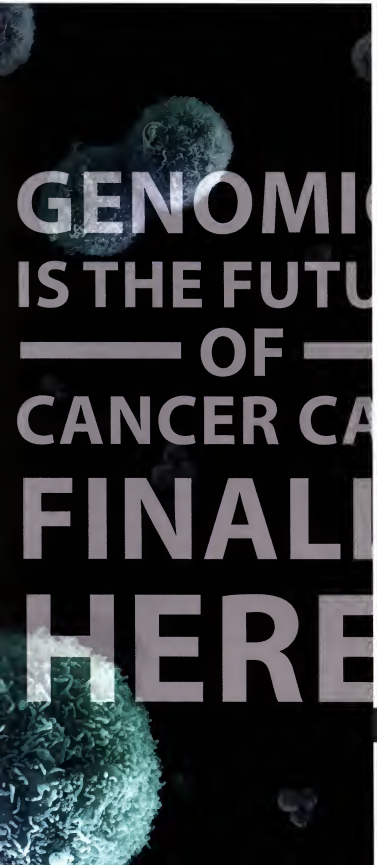
Ursula Hull's physicians used advanced genomic testing as a tool to help develop her treatment plan for lung cancer.



"More **PRECISE** treatments are now possible, including treatments that hadn't been previously considered."

Maurie Markman, MD,
National Director for Medical Oncology and Senior Vice President of Clinical Affairs, CTCA

WE CAN NOW FIGHT CANCER AT A GENETIC LEVEL.

Cancer care has become far more personalized, customized right down to the DNA in the tumor of an individual patient. We can now fight cancer not just by attacking cancer cells, but by reading the DNA contained in the genes of those cells to discover possible treatment options that may not have been considered previously. This may allow for more precise treatment of certain cancers. Advanced genomic testing may allow physicians to discover possible abnormalities in the gene sequences, better understand the DNA alterations driving the growth of a tumor, and then potentially tailor a personalized treatment plan based on the findings.

ADVANCED GENOMIC TESTING ENABLES MORE PRECISE CANCER TREATMENT.

"We can now target therapies specifically against mistakes in a cancer cell's genes," according to Donald Braun, PhD, Vice President of Clinical Research at Cancer Treatment Centers of America ® (CTCA). Advanced genomic testing gives oncologists a snapshot of gene activity within a cancer cell. Genomic testing has been a part of medical science since the human genome was first mapped more than twenty years ago. The real advance is in the significant increase in our understanding of the role specific genes play in the growth and spread of cancer. This has enabled a major advancement in how we approach the treatment of cancer. Until recently cancer has been defined by the organ in which it is first discovered: if it's in the breast, it's been called breast cancer; if it's from the lung, it's lung cancer, etc. Now we realize that one particular type of cancer, say skin cancer for example, doesn't necessarily behave the same as all the other skin cancers. Advanced genomic testing may reveal other treatment options that were not considered previously. For example, now we might treat melanoma with drugs that were created to fight leukemia and do so in a manner

GENOMICS TESTING

HOW IT WORKS

1 A sample of a patient's cancer tissue or biopsy of a tumor is sent to a genomic sequencing lab.

2 Normal genes and genes linked to cancer are sequenced from extracted DNA.

3 Data is analyzed to identify mutations that are critical to certain functions of the tumor.

4 Doctors use lab analysis to find a treatment appropriate for genetic variations identified.

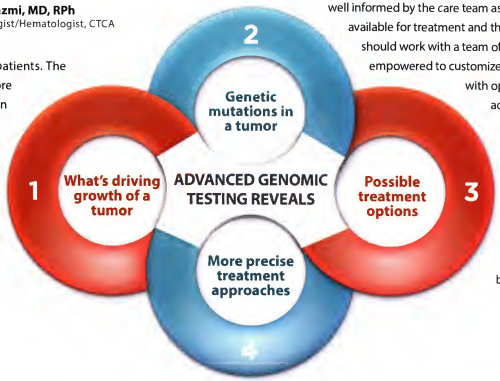
Lung cancer cells as seen in an electron micrographic scan.

Advanced genomic testing. Have you heard of it? Not everyone has, but in the fight against cancer it's an exciting development. It's more than a promise for the future. It's giving hope to many cancer patients today.

"Precision cancer treatment lets us attack with a MISSILE instead of a bomb."

Shayma M. Kazmi, MD, RPh
Medical Oncologist/Hematologist, CTCA

that clearly benefits patients. The ability to design a more precise treatment plan based on the genetic profile of a tumor may create a whole new spectrum of more targeted treatment options and potential new avenues of hope for the patient.



PUTTING THE PATIENT IN CONTROL OF THE CANCER JOURNEY.

Patients should ask if advanced genomic testing is offered at their clinic or hospital, and whether or not it is an option to help guide the treatment plan for their cancer. A patient should always be well informed by the care team as to all the options available for treatment and therapy. Ideally patients should work with a team of oncology experts, empowered to customize a plan of attack with options that include advanced technologies and treatment choice The objective of the treatment plan should be to maintain the patient's quality of life during treatmer with the ultimate goa being full recovery.

Cancer Treatment Centers of America® (CTCA) is a national network of five hospitals in the U.S. with expertise in treating patients who are fighting complex or advanced stage cancer, although many patients with an early stage diagnosis seek treatment at CTCA® as well. We combine world-class treatment with an integrative approach to care to reduce side effects and maintain quality of life during cancer treatment. If you or someone you love has advanced stage or complex cancer call **855-587-5528** *or go to* **cancercenter.com.**

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Care that never quits.®

The Power of Precision Cancer Treatment

Cancer Treatment Centers of America® (CTCA) now offers advanced genomic testing, a form of precision medicine, that may identify cancer treatment options patients haven't considered previously. This innovation reveals the DNA alterations that may drive the growth of specific cancers and may therefore enable more targeted therapies. Visit cancercenter.com to view an informational video on this exciting new development in cancer care.

At CTCA® we believe every patient deserves a personalized treatment plan–one that combines state-of-the-art surgical, radiation, and chemotherapies with nutritional counseling, naturopathic medicine, mind-body therapy, and spiritual support–to help reduce side effects and maintain quality of life during treatment.

If you or a loved one is fighting complex or advanced-stage cancer, please call toll-free at 855-667-7679 or visit cancercenter.com to learn more about the promise of precision cancer treatment.

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By Kevin Davies, PhD

Cheaper, Better, Faster, Stronger

Now that we've cracked the $1,000 genome, where will the DNA-sequencing revolution take us?

In January, the CEO of genome-sequencing company Illumina, Jay Flatley, made a stunning announcement at the J.P. Morgan Healthcare Conference in San Francisco. Introducing his firm's new flagship DNA-sequencing instrument, Flatley declared that this machine would finally deliver the much-ballyhooed "$1,000 genome."

Few observers were more astonished than I. In my book *The $1,000 Genome*, published in late 2010, I chronicled the plummeting cost of sequencing the 3 billion building blocks of DNA that make up the human genome. I imagined we would reach the $1,000 genome in a few years, but not quite so soon.

The "$1,000 genome" catchphrase was coined back in 2001, the same year that two teams published the first drafts of the human genome sequence, an event hailed by presidents and prime ministers as a historical landmark akin to the Apollo moon landing. But those first drafts had taken a decade and cost between $2 billion and $3 billion. Future progress in medicine would require a revolution in DNA sequencing akin to breakthroughs in the computer industry.

Fortunately, a few brilliant scientists were already devising exciting new methods to read the sequence of our genetic code. In 2007, the founder of 454 Life Sciences, Jonathan Rothberg, presented Nobel laureate James "Double Helix" Watson with his complete genome on a DVD. Even though Rothberg said "Project Jim" had cost $1 million, the effort marked the first time that an individual had been presented with his or her personal genome. Watson agreed to release his entire genome to the public, with the exception of a single gene on chromosome 19 called APOE, variants of which are associated with Alzheimer's disease risk.

> "I IMAGINED WE WOULD REACH THE $1,000 GENOME IN A FEW YEARS, BUT NOT QUITE SO SOON."

But 454's days were numbered. After Illumina acquired a British outfit called Solexa in 2007, it steadily strengthened its grip on the sequencing market. This year already, half a dozen organizations have giddily forked over the $10 million for Illumina's newest machines, capable of sequencing more than 150 human genomes in just three days.

Genome sequencing has been transforming clinical medicine since 2009, when Wisconsin geneticist Howard Jacob was asked by a colleague to sequence the genome of a very sick little boy, 4-year-old Nic Volker, who had a mystery

ILLUSTRATION BY MELINDA JOSIE

autoimmune condition. The sequencing identified a critical mutation that ended Nic's diagnostic odyssey and more than 100 fruitless surgeries, gave his doctors the rationale to conduct a bone marrow transplant, and probably saved his life. As Jacob's team continues to sequence the genomes of patients with undiagnosed disorders, several health insurance companies have accepted the economic benefits of genome sequencing and are covering the costs.

Many other medical centers are following suit, including Baylor College of Medicine in Houston, where Christine Eng and colleagues have sequenced the genomes of more than 2,000 patients with suspected genetic disorders, reporting (in a 2013 article in the *New England Journal of Medicine*) a success rate of about 1 in 4.

The sequencing revolution is being felt in other areas, too: Noninvasive testing of fetal DNA in the mother's blood can detect Down syndrome; preimplantation diagnosis can screen IVF embryos for more than 2,000 genetic disorders; and one company, GenePeeks, plans to transform screening at sperm banks by analyzing "virtual" progeny between client and donors. Tumor profiling — identifying mutations in individual tumors and matching the appropriate therapeutic — is taking off. And we haven't even begun to discuss the impact on microbial sequencing, in areas from food safety to emerging diseases and the microbiome (the microbial ecosystem that lives inside our gut and on our skin and that appears to play a crucial role in human health).

As medical doctors prepare to accept the $1,000 genome, it is the "$1 million interpretation" that scares them — in other words, the challenges of interpreting the data (including expertise and IT systems), integrating genome data into electronic medical records, educating physicians lost in the language of DNA, and balancing the benefits of full disclosure versus a patient's right to privacy.

BEYOND THE $1,000 GENOME

The warm reception to Illumina's $1,000 genome announcement is, in part, because Flatley's calculation doesn't just cover the cost of chemicals but also instrument depreciation (over four years), labor, and sample preparation. What it does not include, however, are electricity — which could be useful! — and the cost of storing all that data. Of course, if you can afford $10 million for a new sequencing setup, you must already have a fairly sophisticated data center.

For an individual interested in a full sequence, a good place to start is Illumina's Understanding Your Genome conference. For $5,000, attendees receive their full personal genome presented on a new iPad. Meanwhile, a Belgian startup called Gentle offers personal exome sequencing for about $2,000, with the test ordered through a physician.

Can anyone dethrone Illumina? Not for a while, although one potential threat is British company Oxford Nanopore Technologies. This firm is commercializing the sequencing of DNA using bacterial proteins called nanopores, which are shaped like ring doughnuts. In February, researchers got their first glimpse of data generated by Oxford Nanopore: The sequence of a bacterial DNA molecule was deduced without expensive lasers or cameras, just by measuring the electrical current fluctuations as the DNA strand was threaded through the pore. What makes this especially remarkable is that Oxford's instrument, the MinION, is slimmer than an iPhone and plugs directly into a laptop via a USB cord. I like to carry a prototype around in my jacket pocket just to impress people.

The nanopore system has a long way to go, but regardless of which company drives the market from here on, the future seems clear: DNA sequencing will become cheaper, faster, and more accurate in the coming years. In the words of Johns Hopkins medical geneticist David Valle, personalized medicine will someday be summed up as: "Sequence once, read often."

Kevin Davies is the author of *Cracking the Genome* and *The $1,000 Genome*. He is publisher of *Chemical & Engineering News*, published by the American Chemical Society in Washington, D.C.

By Ide Mills

The Emotional Side of Personalized Medicine

When this patient's lung cancer treatment went from intravenous chemo to a twice-daily pill, it wasn't the relief you might expect.

I have advanced, ALK-positive non-small cell lung cancer with disease in my lungs, lymph nodes, and bones.

Luckily, there's a pill for that.

You would think that taking an oral therapy targeted to my specific type of cancer would make me elated. Compared to chemotherapy, it is more effective, has fewer side effects, and fits easier into my schedule.

Rather, the experience put me in a tailspin. I wrestled with issues of control, how active a role I take in my healthcare, and whether I was ready to be public about having cancer.

Like many people diagnosed with cancer, for the first two and a half years, I lived in three-week cycles. Every 21 days I would see my oncologist and receive chemotherapy. Working as an oncology social worker, health educator, and communication strategist for more than 30 years, I knew it made a difference to be an active partner in my cancer care. The more I know, the more I feel in control of a situation that is irrational. I want to understand the disease and the treatments, as well as what else I can do to help myself live well with cancer.

My activity includes reading cancer articles, searching the internet for credible medical updates, going for treatment, tracking my symptoms and side effects, asking my doctors and nurses questions, thinking about what this all means, and talking a lot. Note that I said "going for treatment." But today, with more than one-fourth of cancer therapies in pill form, it is also accurate to say "taking my medicine."

Herein lies my struggle.

> "WHILE ORAL THERAPY WOULD GIVE ME MORE FLEXIBILITY, HOW COULD I TAKE BACK THE REINS WITH JUST A PILL?"

Intravenous chemotherapy was a visible experience. Along with the treatment came the barrage of side effects — some worse than others, some transient, others permanent. This was the part of the cancer experience I knew all too well when my professional and personal worlds collided. My family and close friends knew when I was going for treatment, and the flurry of questions and support would follow. I talked, and they listened. I described my symptoms, what chemo I was on, how often I would receive it, how it made me feel, how I managed the side effects, when I was getting scanned, and what the results suggested. I recounted what my nurses and doctors said, referenced my cancer team regularly, and told stories about my cancer experience. I saved

ILLUSTRATION BY MELINDA JOBIE

my fears and macabre thoughts for a select few.

Controlled public sharing — I deluded myself by thinking I could do just that. While I shared my cancer life with many, including my work colleagues, I wanted to keep the news from my community and distant relatives. I did not want the head-tilting sigh you get when people hear you have stage 4 lung cancer. Being in control and holding on to some degree of privacy were my goals.

The night before each cycle began, so, too, did my routine. My husband would name the music genre for my chemo party, knowing full well this was no party. I stayed up late as the result of premeds and anxiety, but I used my time efficiently, either doing work or blogging. Day one of every cycle: I worked in the office until it was time to dash off to the cancer center. Hurriedly, I gathered my computer and folders and shared last-minute thoughts with staff, knowing I would not be back in the office until the next Tuesday or Wednesday. "I'll be at the cancer center. Call if you need me." Or, "What time are we doing the conference call?" Family and friends also knew when I was going for treatment. "Do you need a ride? Do you want company?" Everyone checked up on me in the days that followed. As treatment continued, recuperation stretched from three to five days or a week. I received calls and texts daily. "How are you? What can I get you?"

The three-week cycles continued for two more years, as did the outpouring of support. Without the love and attention, IV treatment would have been unbearable. I deeply appreciated everyone listening to my stories or reading my blog. Talking with my private audience helped me deal with my cancer experience.

My story may seem similar to the thousands written before mine. What is different is what I experienced after my cancer progressed. I chose to go on a clinical trial consisting of Xalkori (crizotinib), an oral therapy targeted to my specific type of lung cancer, and an experimental drug given by IV. The new protocol meant new routines, new side effects, new details, and new stories. The scans showed remarkable results, with significant shrinkage of the tumors. I was actively controlling my cancer again.

A few months into the new treatment, lab results forced me to come off the trial. It was a side effect of the experimental drug (the cancer did not progress). Rationally, I was disappointed, and emotionally I felt defeated. The cancer would gain control. Even though I left the clinical trial, I stayed on Xalkori, but it was hard to feel excited that I would only need to take a pill twice a day. While oral therapy would give me more flexibility, how could I take back the reins with just a pill?

I had not yet adjusted to the concept of oral cancer therapy. Family and friends hadn't either. They continued to ask me when I was getting my next treatment.

The responsibility now is mine. I know that. Even though I developed educational programs to help people like me understand the importance of taking their oral cancer medicines as prescribed, it is hard for me to believe that this pill is potent enough to keep the cancer in control. There must be more I can do. Change my diet, exercise, reduce stress? Check, check, check. Am I being active enough? Because I have so much more time taking an oral treatment, these are the questions that fill my day. Anxiety too often fills the void.

The thoughts are haunting: This is cancer, and cancer kills, so I need the big guns to treat it.

Not that I am looking for treatment with harsh side effects, but maybe there is a bit of the no-pain, no-gain theory I am subscribing to.

Thankfully my doctors don't subscribe to that theory. They regularly point out that my side effects are more than I should have to experience. Xalkori has its share of side effects — some transient, some not — but I feel stronger and healthier. As I've adjusted, my schedule now includes working, going to the gym, seeing friends, and cooking nutritious meals. Okay, I don't get to the gym every day, but I get there more than when I was on an IV chemo regimen. With the help of my social worker, I have come to accept that I am taking enough of an active role in my cancer care — medically and non-medically.

The routine is more private. There are fewer stories to tell. I've found, though, that the care and compassion from my family and friends remain a constant. I may talk less about the cancer and my treatment, but they still ask how I am doing. I think that is partly why I was worried about being on an oral therapy. Would people forget that I get frightened every time I have a scan? I face tremendous anxiety every 12 weeks, even if I don't announce it or report my results. While I am responding well to treatment and feeling healthy, I don't walk my family or friends through all the details. It's more of an update — part of the conversation, not the focus.

It would be easier now to be private about my cancer, but I have decided to be completely public. It is time for me to help others and share my perspective on living with a chronic, life-threatening illness. The face of advanced lung cancer has changed, ever so slightly. I hope my face, physical stamina, emotional strength, and voice can give hope to others living with cancer and facing new emotional challenges with the advances in targeted treatment. My tailspin has passed, and I am glad to be taking a pill twice a day.

Ide Mills works as a healthcare consultant, patient advocate, and oncology resource when she's not working at being a wife and mother of two grown children.

By Aimee Swartz

A Fetal Development

Prenatal DNA testing of a small sample of blood reduces the need for invasive procedures to detect Down syndrome and other genetic disorders. But that's only the beginning of what these tests will be able to do.

When Abby Brown became pregnant at 35 with her first child, in 2012, she knew that her age put her fetus at an elevated risk for Down syndrome. At age 25, a woman's odds of having a baby with the disorder are 1 in 1,200. Those odds climb to 1 in about 350 by the age of 35 and to 1 in about 40 by age 44.

Blood tests typically used to screen for Down syndrome had raised no red flags for Brown, now 37 and living in New York City, but still she wanted to be certain that her fetus was healthy. Each year in the United States, an estimated 6,000 babies are born with Down syndrome, a chromosomal abnormality that causes lifelong mental disabilities, developmental delays, and, often, heart defects and other health problems.

Until recently, ruling out a diagnosis of Down syndrome and other chromosomal abnormalities prenatally required amniocentesis or chorionic villus sampling—invasive procedures that require the insertion of a needle or tube into the womb or placenta and cause 1 to 2 percent of women to have a miscarriage.

Brown and her husband faced a complicated decision: risk a healthy pregnancy to find out for sure if there was something wrong with their child or live with a degree of uncertainty? Then Brown learned about a new option that had come on the market just weeks before: a screening test that is about as accurate as amniocentesis and chorionic villus sampling but as low-risk as a routine blood draw.

Known as fetal cell-free DNA testing (cfDNA), the test can detect Down syndrome and other chromosomal abnormalities through a sample of blood drawn from the mother.

Chromosomal abnormalities are caused by a missing, extra, or irregular chromosome. Typically, humans have 46 chromosomes in every cell of their body—23 inherited from their mother and 23 inherited from their father. People with Down syndrome have three copies (trisomy) of chromosome 21 instead of the usual two.

The cfDNA tests rely on DNA fragments shed by the placenta that, in nearly all pregnancies, are equivalent to fetal DNA. These short fragments of DNA, along with fragments from the pregnant woman, float in the woman's bloodstream. This mixture of fragments can be extracted and analyzed for extra material from specific chromosomes.

"If more than the expected proportion of fragments for chromosome 21 are found, for example, it would indicate that the fetus may have Down syndrome," says Glenn Palomaki, a scientist specializing in prenatal screening at Women & Infants Hospital and Alpert Medical School at Brown University in Providence, Rhode Island.

ILLUSTRATION BY SHOUT

In addition to screening for Down syndrome, cfDNA tests can also screen for Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13), both of which can cause serious developmental and medical issues. Some insurance plans cover the tests, which cost anywhere from $500 to $2,000, but most patients wind up paying out of pocket.

Though prenatal screening tests vary by clinic, the current standard often includes a blood test and an ultrasound during the first trimester. The blood test measures certain hormone and protein levels that are associated with chromosomal abnormalities. The ultrasound, called a nuchal translucency test, measures the fluid that accumulates in the back of a fetus's neck — a characteristic that is strongly associated with an elevated risk of Down syndrome.

These standard screening tests estimate the chance of the fetus having Down syndrome, but they neither confirm nor rule out the disorder. Women deemed to be at high risk based on the screening are advised to undergo either amniocentesis or chorionic villus sampling for a definitive answer.

The problem with routinely used tests, says Diana Bianchi, executive director of Tufts Medical Center's Mother Infant Research Institute, is that "they are far from definitive." Large studies have shown that these tests pick up only about 79 to 90 percent of all cases of Down syndrome and incorrectly detect the disorder — an occurrence known as a "false positive" — in about 3 to 6 percent of all cases.

In contrast, cfDNA tests are "extremely accurate," Palomaki says. Recent data show that cfDNA tests can identify 99 of every 100 fetuses with Down syndrome. Just as important, he notes, is that cfDNA tests incorrectly identify Down syndrome in only 1 in 200 normal pregnancies — much lower than typical screening methods, which incorrectly identify Down syndrome in as many as 12 in every 200 normal pregnancies.

At the time of Abby Brown's pregnancy, the technology was so new that only a few clinics in London, where she lived at the time, offered cfDNA testing. Once she located a clinic near her that offered the tests, she did not hesitate to make an appointment. Within a week, Brown learned that she had less than a 1 in 10,000 chance of having a child born with Down syndrome.

Fetal cell-free DNA testing is not perfect, however. If blood samples do not include sufficient placental DNA, the results may be inconclusive. And a rare form of Down syndrome called mosaicism, in which abnormalities can vary between the placenta and the fetus, can be missed by cfDNA tests.

Bianchi points to the fact that cfDNA testing can be done as early as the seventh to ninth week of pregnancy as one of the technology's "greatest advantages," saying it gives women and their partners "more time to grapple with the difficult choice of terminating a pregnancy or preparing for a special-needs child."

Others say that the ability to detect a problem so much earlier than amniocentesis — typically performed between the 15th and 20th weeks of pregnancy — could result in more women choosing an abortion. "It may seem more acceptable to women than having an abortion much later in their pregnancy," says Arthur Caplan, a professor of bioethics at New York University's Langone Medical Center.

Because of the chance of a false positive, women are advised not to base their decision to terminate their pregnancies on results of cfDNA testing alone. Rather, Bianchi says, "Those who test positive are very strongly urged to undergo an amniocentesis or chorionic villus sampling before taking irreversible action."

Though cfDNA testing cannot completely replace invasive diagnostics, Caplan says, "It won't be long before it becomes standard of care for all women."

Bianchi estimates that well over 100,000 tests have been performed. And in late 2012, the American College of Obstetricians and Gynecologists began recommending cfDNA testing as a screening tool for women at high risk of delivering a baby with Down syndrome.

The rapid uptake of cfDNA tests suggests they are likely just the beginning when it comes to prenatal DNA screening. Though sequencing the fetus's entire genome using cell-free DNA fragment is still too expensive to be done under normal conditions, with the costs of genome sequencing continuing to fall, some foresee a future in which information about a fetus extends well beyond a handful of known fetal conditions to any human trait that has a major genetic component.

"What if we are able to detect a gene that increases the risk of a disease — for example, breast cancer? What if we can detect deafness or short-statuedness?" Caplan says. "This really has the potential to change the way people think about pregnancy in general. Genetic counselors are going to become very, very important." 4.

Invasive No More

Four fetal cell-free DNA tests are available in the United States

Harmony Prenatal Test
Ariosa Diagnostics' Harmony Prenatal Test screens for Down syndrome, Patau syndrome, and Edwards syndrome. The test includes an optional analysis of sex chromosome conditions such as Klinefelter syndrome and Turner syndrome. Sex chromosome conditions occur when there is a missing, extra, or incomplete copy of one of the sex chromosomes. *ariosadx.com*

MaterniT21 PLUS
Sequenom's MaterniT21 PLUS test screens for Down syndrome, Patau syndrome, Edwards syndrome, sex chromosome conditions, and other more rare conditions. *laboratories.sequenom.com*

Panorama Prenatal Test
Natera's Panorama test screens for Down syndrome, Patau syndrome, and Edwards syndrome. It also screens for sex chromosome conditions and triploidy, a rare chromosomal abnormality in which a fetus has an extra set of chromosomes. *panoramatest.com*

Verifi Prenatal Test
The basic version of Illumina's Verifi test screens for Down syndrome, Patau syndrome, and Edwards syndrome. A wider option is also available to screen for sex chromosome conditions. *verifitest.com*

By Eric Celeste

What Would Your GC Do?

They can't answer that. But a certified genetic counselor can give you the information you need to navigate the difficult decisions genetic disease testing often brings about.

IT HAPPENED MANY YEARS ago, but Erynn Gordon remembers clearly when the 25-year-old mother she was counseling said she was going to have a hysterectomy. Gordon, a genetic counselor, was working at a neuromuscular clinic, and the young mother's only child had just been diagnosed with Duchenne muscular dystrophy — a frightening, lethal disease affecting boys. It is linked to the X chromosome, and males who have it (they're usually diagnosed between 3 and 5 years of age) die in their 20s after progressive muscle deterioration leaves them paralyzed, albeit cognitively normal.

The mother was devastated. She wanted to be certain she would never pass on this genetic defect to another child. Even the thought of prenatal testing offered her no hope, as she was deeply religious and would never terminate a pregnancy.

Gordon asked the understandably distraught mother to postpone making such a dramatic decision. Gordon told her that although the prognosis for her son could not be changed, she might one day want other children. She told the young mother about a sperm-sorting technology that could filter the sperm based on whether it carried an X or a Y chromosome. It's used pre-conception, and the mother could then be inseminated with X-bearing sperm, which would preferentially select for a girl (who could be a carrier for the disease but would not be affected).

Erynn Gordon helped design the certification test for genetic counselors.

"Ultimately, that's what the family chose to do," says Gordon, a longtime genetic counselor now on the clinical team at genetic testing company Invitae, based in San Francisco. "'What would you do?' is a question

PHOTOGRAPH BY CHRIS SEMBROT

that genetic counselors are trained to never answer. Like in this case, the things we're talking about with patients are very personal decisions, ones that can have severe ramifications. We're there to give all the information they need to make that decision, but it's vital we don't make them feel shamed or that we don't approve of the decision. Because the right answer is different for everyone."

This case is a glimpse into the daily ethical, medical, and moral dilemmas genetic counselors help patients navigate. The endings aren't always happy. (In fact, after two sperm-sorting attempts failed to result in a pregnancy, the couple had another boy who was DMD positive.) But counselors like Gordon, past president of the American Board of Genetic Counseling, know there is tremendous value in giving patients the information they need to make informed decisions, even if some paths offer only degrees of distress.

Genetic counselors say this is a critical time for their profession. Even though counselors have been under a spotlight since Angelina Jolie's public decision last year to have a double mastectomy after genetic testing, people still don't have a clear understanding of what counselors do and what they don't do. Because of this, patients are often unaware of the nesting boxes filled with questions that genetic testing often presents — and the need for GCs to help them thoughtfully meet each demand.

ACCORDING TO THE AMERICAN BOARD OF Genetic Counseling, as of press time, there are only 3,193 certified genetic counselors in the country. States rely on this certification as a benchmark for licensure, which is a relatively new process. This process is an attempt to protect the public from folks who would call themselves genetic counselors without the training to do so.

The profession is in dire need of new counselors for three main reasons: Patients and doctors are becoming more familiar with a genetic, personalized approach to medicine, driving demand for more genetic testing and thus more counseling to interpret those tests; more consumer companies are offering genetic testing (often with minimal ability to put those tests in context for consumers); and medical technology continues to develop, allowing for more diagnoses and treatments based on genetic information.

> “OFTEN PATIENTS THINK BECAUSE OF HOW ADVANCED GENETIC TESTING IS NOW, THEY WILL GET AN ANSWER, BUT THAT'S NOT ALWAYS THE CASE.”

By their nature, genetic breakthroughs require distinct areas of specialization on the part of genetic counselors to understand and communicate with patients as well as other members of the healthcare team. That's why most genetic counselors end up in non-primary care settings — working at a laboratory or specializing in patient categories (prenatal, pediatrics, adult onset) or disease type/location (cancer, cardiology, neurology).

Meg Menzel, a senior genetic counselor at Children's National Medical Center in Washington, D.C., has been a practicing GC for 14 years. Her background is not unlike most genetic counselors in that she has done “a little bit of everything” — counseling everywhere from a hospital in New York City to a cancer center to the office of a private geneticist. Although she has counseled at adult and pediatric offices, she now focuses on prenatal medicine. Her path mirrored the industry's. Where one used to see genetic counselors mostly in large academic hospital centers, now there are many in more private-practice settings.

“Post-Jolie,” counselors say they are busier than ever, although they also deal with more false preconceptions than before the actress highlighted the work they do. Most see six to eight patients a day for counseling sessions that vary from a half-hour to two hours. Realizing there is no “typical” counseling session, most appointments consist of at least three components: a discussion of family history (often focusing on hereditary diseases or conditions); a look at what current tests or

What Is Genetic Counseling?

The goal of genetic counseling is to help you learn more about the causes of genetic conditions and how they affect you. **Genetic counselors can:**

- Review your family and medical histories.
- Explain how genetic conditions are passed down through families.
- Figure out if you or your family members are at risk for disease.
- Find and give you information about genetic conditions.
- Offer guidance to help you make informed choices or life plans.
- Provide information about testing options and help you decide what is best for you and your family.
- Help you find referrals to medical specialists, advocacy and support networks, and other resources.

—American Board of Genetic Counseling

diagnoses have shown (example: Are seizures indicative of a possible genetic condition?); the screening or testing options available (for instance, a pre-conception test to see if the cousin of someone with cystic fibrosis is likely to have a child with CF); and the implications of a patient's decision.

Throughout such sessions, counselors look for patterns beneath the surface, beyond obvious associations such as "I have a great-aunt with breast cancer." As they search for constellations of symptoms that might travel together, every aspect of the session can become vital.

Some decisions are straightforward. You're a male in your 40s, and you tell your counselor there is a history of drowning in your family, even though they were good swimmers. The counselor suspects a hereditary arrhythmia syndrome, which tests conclude is accurate. Your medical team recommends you implant a defibrillator, which one day saves your life.

MORE OFTEN, THOUGH, THE ISSUES raised by genetic counseling — or, more specifically, by a lack of genetic counseling — and testing are more complex and the results less assured. One common problem is that of "incidental findings."

Menzel gives an example: A 3-year-old child with developmental delays is brought into a pediatrics clinic, and standard testing reveals nothing unusual. The doctor then orders a whole genome sequencing test to find every possible mutation that could be causing the delays. The parents, who are wealthy enough to afford this expensive process, hope they'll get a magic answer. But the lab doing the sequencing doesn't filter out (as many labs do) information that shows adult-onset results. The lab results ultimately show nothing that reveals why the child is having developmental delays, but they do show a BRCA mutation, a gene mutation associated with risk of breast and ovarian cancer. And, as Amy Sturm, a certified genetic counselor and associate professor of internal medicine at the Wexner Medical Center at The Ohio State University, notes, new guidelines from the American College of Medical Genetics and Genomics say specific incidental findings should be reported to patients. In such a case, medical, psychological, and insurance concerns will flood the unsuspecting family.

"It's irrelevant to the clinical presentation, but now we've raised this tremendous other problem, with information the parents could have decided they wouldn't want to know at this point," Menzel says. She says she would have offered the parents the right to opt out of receiving adult-onset information or suggested a lab that weeds out that information.

Sometimes the challenge is just the opposite. All the technology and guidance in the world can't give patients a good answer — or at least an obvious answer — as to what's best for their case, or sometimes even what the disease is. The concern, Menzel says, is that post-Jolie, many patients have a better understanding (and are more often seeking) genetic *testing*, but not counseling.

"Often patients think because of how advanced genetic testing is now, they will get an answer, but that's not always the case," she says. "It's very tough with prenatal, for example, because often the best we can do is look through the mom. We can see the baby has five fingers, but we have no idea if they're moving properly. If we test and the baby has Down syndrome, we know what that means. We know the spectrum of the disease. But if we do test and all our tests come back normal, but we're seeing imaging issues that concern us, we have an unknown, and that's still the biggest challenge. Because even with whole exome and whole genome sequencing taking off, much of the time the mutations we see in genes, we still don't know what they mean."

How Can I Find a Genetic Counselor? Go to the website for the National Society of Genetic Counselors at **nsgc.org** and use its online tool for finding a certified or licensed genetic counselor near you.

Counselors say the trickiest part of their job could be navigating the delicate tensions that arise in families when discussing heredity and disease. "A lot of the conversations revolve around encouraging people to share their information, especially when the findings could affect other family members, so that other people can then decide if they want to be tested," Gordon says. "But some people don't want to share. They don't want to be responsible for delivering that information. You can give them resources that allow them to do that, but sometimes your hands are tied."

Such conundrums are frequent, especially in a pediatric setting. How do you communicate disturbing findings to children? When is the right time to do so? What if one child is affected but his sibling is not? What if there is a 50 percent chance your daughter is a carrier for a disease? When do you tell her? Do you test her? At what age?

Those difficulties aside, it's such discussions, not simply the testing, that form the foundation of genetic counseling.

"The time we spend with families is huge," Menzel says. "Doctors don't have the time. We do. One hour, two. It's necessary to go over all these concerns families don't see before they come in. Sometimes families who've done all the research come in and still don't yet see the ethical concerns, the potential drawbacks, to the decisions they're going to make. We help them make informed decisions. That's the rewarding part."

Why Might I See a Genetic Counselor?

- You are pregnant or considering becoming pregnant and are concerned about the health of your baby.
- Your baby had an abnormal result from newborn screening.
- You, your child, or a family member has been diagnosed with a genetic condition.
- You are concerned that you, your child, or a family member has a genetic or inherited condition and would like more information.
- Your family has a history of developmental disability, birth defects, and/or mental retardation.
- Your family has a history of mental illness.
- Your family has a history of cancer.

—American Board of Genetic Counseling

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We're here for you during each step of your journey. Better answers. Better health.

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Baby's First Test informs and empowers families and healthcare providers throughout the newborn screening experience. By increasing awareness and providing a one-stop shop of all newborn screening information, we offer millions of newborns and their families a chance at a healthy start.

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Disease InfoSearch puts information on thousands of diseases at your fingertips, including the latest research, clinical trials, and available support. Whether you're looking for yourself, a family member, or a patient, you can find the information you want and the support you need.

PEER

Platform for Engaging Everyone Responsibly (PEER) provides an interactive experience and gives you the tools to set your own health information, sharing, privacy, and access preferences. Get connected to support and medical research on your own terms!

Get Started Here: GeneticAlliance.org | BabysFirstTest.org | GenesInLife.org | DiseaseInfoSearch.org | Reg4ALL.org

By Leslie Minora

The Rise of Pharma-lanthropy

An increasing number of nonprofit foundations are partnering with pharmaceutical companies to speed development of targeted treatments for cystic fibrosis, Parkinson's, leukemia, and more.

As a pediatric intensive care nurse at MassGeneral Hospital for Children, Kimberly Cheevers cared for cystic fibrosis patients in varying degrees of health. She saw how the inherited disease, which causes thickened mucus in the lungs, pancreas, and intestines, made patients prone to severe respiratory infections. She saw children coping with symptoms but living relatively normally; in other cases, she saw the disease at its worst, ending lives that had barely started.

As a mother, Cheevers cares for two daughters, 15-year-old Laura and 12-year-old Cate, who were both born with cystic fibrosis. She and her husband are carriers of a gene mutation that causes the disease, but they do not have it themselves. Odds were low that both daughters would suffer from it. When that ultimately became the case, Cheevers' colleagues at the hospital shielded her from nursing other patients with the disease.

Devastated. That's how she felt at her first daughter's diagnosis. At the time, available treatments reduced symptoms and lengthened life expectancy, but only to patients' late 30s. Cheevers learned from her doctor that promising treatments were developing, and she clung to that hope. Meanwhile, the Cystic Fibrosis Foundation was funding research for targeted drugs aimed at correcting the disease's genetically dictated cellular malfunctions.

At around the time Cate was born, the Cystic Fibrosis Foundation began a novel approach, investing tens of millions of nonprofit dollars over several years to fund commercial pharmaceutical research. Over time, this venture philanthropy model caught on as more nonprofits adopted similar strategies, including organizations dedicated to finding treatments for Parkinson's disease, multiple myeloma, and juvenile diabetes. The financial risk of funding pharmaceutical research is high, but the implications for more specialized disease treatment are vast.

For the Cheevers girls, every day of childhood meant a barrage of enzymes, vitamins,

ILLUSTRATION BY OLIVER MUNDAY

physical therapies, nebulizer treatments, and, at times, antibiotics. For many years, coughing made it difficult to sleep at night. Yet, even with constant treatments and interruptions, both girls managed lives full of friends and activities, and they excelled in school.

Still, bouts of illness would periodically sideline the girls from everyday life. Laura was hospitalized several times for a "clean-out" with high doses of antibiotics to treat infection. Gradually, the bacteria in her lungs became resistant; there were increasingly fewer effective antibiotics. This worried her mother. With Cate, there was plenty of coughing, but complications were less severe.

Cheevers wanted to do everything she could to ensure cystic fibrosis research was funded and expedient. "I couldn't find a cure; I'm not a scientist. But I'm connected, and I'm eager, and I'm hardworking," she says. She began fundraising for the Cystic Fibrosis Foundation and, working with other families like hers, has raised more than $1 million.

IN 1989, LONG BEFORE LAURA AND CATE were born, a genetic cause of cystic fibrosis was discovered through research supported by the Cystic Fibrosis Foundation. For a moment in history, it seemed that the newly pinpointed faulty gene would reveal an obvious cure. Instead, further research showed that there are nearly 2,000 distinct mutations in that gene that could cause the disease, meaning a cure was much more complex.

As CEO of the Cystic Fibrosis Foundation, Robert Beall, a former biochemist, has always had his sights set on a cure. To him, that means reducing the financial risks of early-stage drug development through investments in pharmaceutical research. In 2000, he led the foundation to launch Cystic Fibrosis Therapeutics Inc., the part of the organization dedicated to drug discovery through collaborations with for-profit companies.

"It grew out of frustration. ... The biggest risk for us was not taking an opportunity to move forward," he says. The thinking was: "If we don't do it, no one will."

According to Richard Hamermesh, a Harvard Business School professor and chair of the school's Healthcare Initiative, the cause of Beall's frustration and the need for his funding are tied to the fact that early-stage biotechnology investment money has gradually been drying up, especially following the economic recession. "So the question is: Who is going to fill that gap?" he says. Increasingly, the answer is nonprofits like the Cystic Fibrosis Foundation.

Joe O'Donnell, a successful Massachusetts businessman and philanthropist who lost his 12-year-old son to cystic fibrosis in 1986, started The Joey Fund, which primarily funds biotech research and also provides assistance to families caring for children with the disease. The charity is independent but inseparable from the Cystic Fibrosis Foundation. O'Donnell is chair of the organization's Milestones to a Cure fundraising initiative, which has pumped more than $175 million into medical research, education, and care. Clearly, this is no small endeavor.

In 2000, the Cystic Fibrosis Foundation began its collaboration with Aurora Biosciences, which was later acquired by Vertex Pharmaceuticals. The company had laboratory technology capable of a high level and volume of testing small-molecule drugs. Beyond the funding stream, the foundation also had connections to patients for clinical trials of these highly specific treatments.

Through the research at Vertex, one compound, VX-770, which would later be called Kalydeco, surfaced first as the most promising development. Clinical trials began in 2006. Kalydeco targeted a specific chromosomal mutation — G551D — that causes about 4 to 5 percent of cystic fibrosis cases by preventing chloride from passing through otherwise intact cellular protein passages.

CHEEVERS RECALLS IT WAS SOMETIME IN 2009 or 2010 when she first heard mention of this new medication and its upcoming clinical trial. About six months later, her daughters' doctor at MassGeneral approached them about participating in a study of VX-770.

Not only was the study taking place at the hospital where Cheevers worked and took her children, but also both girls had the exact chromosomal abnormality, G551D, that the treatment targeted.

"It was like a needle in a haystack," Cheevers says. "It was a complete miracle for us, actually." But it was a trial; the twice-a-day pill was promising but unproven.

On top of that, she says, "It was a double-blind study, so we just didn't know who was getting what." Within six weeks, Cate had more energy, her cough essentially disappeared, and her pulmonary function test, which gauges lung capacity, improved dramatically. She gained 16 pounds in six months.

But Laura, whose condition was more severe, remained the same. After the 48-week

> "THERE'S JUST SO MUCH MORE INTEREST IN THE CONCEPT OF VENTURE PHILANTHROPY. WE'RE ALL IN THIS TOGETHER; THERE'S ROOM FOR A LOT OF PEOPLE TO PARTICIPATE IN THIS."

trial, they found out that she had been given the placebo. She then began taking the medication and gained 10 pounds in six months. Her symptoms improved dramatically. The entire family began sleeping much better. Colds and flus were no longer cause for alarm, and now Cheevers can't recall the last time either daughter was on an antibiotic.

In 2012, the FDA approved Kalydeco, the drug formerly known as VX-770 and generically as ivacaftor.

Laura is on the dance team and runs track. Cate plays basketball and soccer. Even with Kalydeco, they continue taking enzymes and vitamins, more as a precaution, and they use a nebulizer a few times a week instead of at least once daily. Cheevers is stunned by the turnaround.

"I think this is just the beginning ... and I don't think it's a cure right now, but I do think it's a fabulous treatment," she says.

BEALL, OF THE CYSTIC FIBROSIS FOUNdation, is widely considered the founding father of the venture philanthropy model. The success of Kalydeco, which treats the underlying causes instead of just symptoms, fuels the foundation's desire to stay on course pursuing research opportunities with the biotech industry. It also helps financially. The foundation receives royalties on the sales of Kalydeco and reinvests that money in similar research.

Now that Kalydeco has been released, "There's just so much more interest in the concept of venture philanthropy," Beall says. "We're all in this together; there's room for a lot of people to participate in this."

To some, a nonprofit funding for-profit research may seem like a betrayal of the charitable spirit. Yet, it's a major step in treating diseases, especially those that aren't widespread enough to attract commercial investors. O'Donnell, of The Joey Fund, tends to approach such concerns head-on: "You've got a better idea?"

"There's no guarantee we're going to get that other 95 percent," O'Donnell says, meaning the majority of cystic fibrosis patients for whom Kalydeco is not currently considered

7 Nonprofit Groups Using the Venture Philanthropy Model To Help Fund Drug Development

1.

Cystic Fibrosis Foundation

In almost all discussions of venture philanthropy, the Cystic Fibrosis Foundation is upheld as the organization that pioneered the model for rare diseases and has been most successful with it. Its drug development model aims to reduce the financial risk of early-stage drug development of targeted treatments by working with pharmaceutical companies and reinvesting the resulting funds into further research. The discovery and approval of Kalydeco, which treats a root cause of the disease, was a major milestone, and the science behind it has unlocked new research and development that may eventually lead to a cure for cystic fibrosis. cff.org

2.

Michael J. Fox Foundation

Michael J. Fox established his namesake foundation with the goal of developing better treatments and finding a cure for Parkinson's disease. As part of its efforts, the organization has invested $100 million in funding nearly 225 pharmaceutical-industry projects. As with many other organizations, the Michael J. Fox Foundation's pharmaceutical partnerships are part of a nuanced approach that offers funding, research tools, networking, and recruitment assistance for clinical trials. michaeljfox.org

3.

Multiple Myeloma Research Foundation

As part of a widespread approach, the Multiple Myeloma Research Foundation partners with the pharmaceutical and biotech industries to develop new treatments. The organization funds early-stage development, which is often a prohibitively expensive step in pursuing targeted disease treatments. The MMRF Biotech Investment Awards program began in 2006 and has committed $11 million to biotech research and development. Research funded by the MMRF resulted in several new treatments, with more than 20 others in various stages of clinical trials in the development pipeline. themmrf.org

4.

JDRF

JDRF, the leading global organization funding type 1 diabetes research, focuses on translating research into therapies that will improve lives and eventually cure type 1 diabetes. With an approach that includes partnering with pharmaceutical companies, the goal is to "decrease barriers to commercial development." The organization pursues this goal through key partnerships with "the academic sector, NIH [National Institutes of Health], other funders and foundations, industry, investors, regulatory agencies, and healthcare payers" to deliver treatment breakthroughs to patients. jdrf.org

5.

Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society partners with several organizations, including Onconova Therapeutics, Celator Pharmaceuticals, and Acetylon Pharmaceuticals, to expedite the drug-development process. The organization's Therapy Acceleration Program, launched in 2007, funds initiatives with potential to change and accelerate the standard care for patients with blood cancer. The program aims to shepherd therapies from discovery to clinical testing to

increase the likelihood of a beneficial treatment reaching the market. Through its partnership with Onconova, LLS funded a phase 3 clinical trial for patients with relapsed or refractory myelodysplastic syndrome, a type of blood cancer. This marks the organization's first "approval-track clinical trial." lls.org

6.

Alzheimer's Drug Discovery Foundation

The Alzheimer's Drug Discovery Foundation is a biomedical venture philanthropy nonprofit aimed at developing treatments, and eventually a cure, through a diverse portfolio of programs. The ADDF focuses its funding on early-stage research and clinical trials to reduce the financial barriers that prevent promising medications from reaching the public. Many of its grants are structured as investments; the returns are then directed toward new research. The ADDF partners with Merck, Pfizer, and others. It funded early research for what became Amyvid, a diagnostic test for Alzheimer's disease that was approved by the FDA in 2012. alzdiscovery.org

7.

Autism Speaks

Autism Speaks advocates for autistic individuals and funds research to further understand the condition and develop treatments that could lead to a cure. In 2012, it launched Delivering Scientific Innovation for Autism (DELSIA), an independent nonprofit affiliate. DELSIA works with for-profit organizations, including biotech companies, to expedite the development of treatments, devices, diagnostic tools, and other products. As with many venture philanthropic arrangements, its partnerships include profit-sharing arrangements for successful products, and any returns are directed toward further research and development. DELSIA is an additional approach to the scientific research already funded by Autism Speaks. It aims to convert laboratory research into practical applications for those with autism spectrum disorder. autismspeaks.org

a silver bullet. Then, he adds, "But if you're a betting woman, you may want to get your money on that."

With cases like the Cheevers girls as a testament to what this research can accomplish, it's certainly an appealing bet. Or, as O'Donnell puts it, "Kids are breathing like racehorses now."

In late February, the FDA approved Kalydeco for the treatment of eight additional cystic fibrosis mutations, significantly widening its scope. Other clinical trials are underway for drug combinations that include Kalydeco and other compounds, and that could have treatment implications for a greater number of cystic fibrosis patients. The development of one treatment, it seems, is working as a springboard for the development of others.

Another organization taking a similar approach is the Multiple Myeloma Research Foundation. Its founder, Kathy Giusti, is in remission from multiple myeloma, a fatal blood cancer. Diagnosed in 1996, when she worked for pharmaceutical company G.D. Searle, Giusti looked to the pharmaceutical pipeline to see whether any promising treatments were in development. Unfortunately, she didn't find much hope. This "silent killer," as she calls it, needed the attention of biotech developers.

A Harvard Business School graduate with pharmaceutical experience, Giusti knew what had to be done and how to do it. Her foundation went on to develop a genomic initiative that increased the basic biological understanding of the disease. With genetic targets in mind, the foundation funds early-stage pharmaceutical research. Like the Cystic Fibrosis Foundation, Giusti's organization takes a widespread approach, pursuing treatment models for multiple variations of the disease simultaneously.

As for the progress that has been made, Giusti says, "We've already conducted nearly 50 phase 1 and 2 trials. We've seen six drugs approved by the FDA." The five-year survival rate for multiple myeloma patients has also more than doubled in the past 10 years.

FasterCures, an organization with a mission to "remove barriers to medical progress," acts as a repository of information and resources. It emerged in 2003 as an information-sharing hub for best practices, including those related to partnerships between nonprofits and pharmaceutical companies. Over the past several years, the National Institutes of Health, the FDA, pharmaceutical companies, and academic researchers have become keenly aware of certain disease-based nonprofits and the research funding and clinical trial participants they can provide, says FasterCures Executive Director Margaret Anderson.

> "I THINK THIS IS JUST THE BEGINNING... AND I DON'T THINK IT'S A CURE RIGHT NOW, BUT I DO THINK KALYDECO IS A FABULOUS TREATMENT."

Referring to partnerships between nonprofits and pharmaceutical companies, Anderson says, "It's not that it's a marriage of convenience; it's a marriage of necessity. There's an increasing awareness of that."

This partnership method of pharmaceutical development is a constant balance of risk and potential. And even when a drug like Kalydeco is developed, there's a realization of how much more is needed.

Still, there are people like Laura and Cate, who are living proof of what's possible. Their mother sees the potential every single day. "Never give up when you're faced with something like this in your life," Cheevers says.

IT'S CHANGING THE WORLD OF HEALTHCARE. WHAT YOU NEED TO KNOW ABOUT THE MOVEMENT FUELED BY GENOMIC TESTING AND TAILORED TREATMENT.

WHAT IS

PERSONALIZED MEDICINE?

By Dawn McMullan

PHOTOGRAPHS BY ADAM VOORHES

YOU GO TO YOUR DOCTOR
WITH YOUR SYMPTOMS,
AND YOU GET AN EVALUATION,
MAYBE HAVE A FEW TESTS RUN.

If you are lucky, you're on your way to a diagnosis and a path to feeling better. How much more personal does it get? In fact, much more. In theory, astonishingly more.

Most often today, your treatment plan doesn't have all that much to do with you specifically. It's identical to what doctors would hand over to essentially anyone with the same condition — your neighbor, the hot dog vendor at Wrigley Field, or the prime minister of Bangladesh.

That's because medicine as we know it revolves around "standards of care," the best courses of prevention or treatment for the general population, or the average person on the street. With breast cancer, for example, those standards mean self-exams and mammograms after a set age and the usual chemotherapy to treat a tumor if one is found. If the first treatment doesn't work, doctors and patients move on to the next one and the next. It's trial and error, with life on the line.

A growing contingent of researchers, some healthcare clinicians, and an increasing number of patients are calling for a more personalized approach aimed as much at preventing disease as it is at tailoring treatment once it's there. Call it what you will — personalized medicine, genomic medicine, precision medicine. It's an approach that emphasizes the ways in which your disease risks are unique and different, just like your other, more obvious characteristics. Those disease risks are based on the predispositions written into your genome at birth, combined with your lifestyle and environment. In the case of cancer, the disease has its own genetic makeup, lending each tumor a unique character with unique tendencies and vulnerabilities.

And perhaps there is, or soon will be, a drug or treatment or tailored combination of the two that will work better for you than it would for someone else.

"The number of targeted therapies in the pipeline for all diseases is increasing dramatically," says J. Leonard Lichtenfeld, deputy chief medical officer for the American Cancer Society. "Personalized medicine in the age of genomics means we're living in dynamic times. The big question right now is 'How do we take all this new information we're gathering and use it for the benefit of the patient?'"

In many cases, the current standard of care may be the safest, most sensible option, but it's also "one size fits all." Sometimes that's perfectly sufficient, but not always. It is in that "not always" category that personalized medicine is making the most headway.

A DECADE OF ADVANCEMENT

Many doctors will tell you they've been doing personalized, patient-centered medicine all along, and they do have a point. Wikipedia defines personalized medicine as "a medical model that proposes the customization of healthcare — with medical decisions, practices, and/or products being tailored to the individual patient." But the definition preferred by the National Human Genome Research Institute is more specific, maintaining that a personalized approach to medicine includes an "individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease." Reaching that goal has been more than 20 years in the making, birthed from an ambitious plan to sequence the first reference human genome. By 2003, scientists had done it; for the first time, they had an essentially complete sequence and map of all the genes in the human body.

"Probably at no time in the history of medical research, going back to the time of William Harvey and the circulation of blood, in the 1600s, has there been more potential and promise for discovery that will benefit mankind in terms of the health of the species as where we are right now as a result of the Human Genome Project," says Scott T. Weiss, scientific director at Partners HealthCare Center for Personalized Genetic Medicine at Harvard Medical School.

Advances in technology have since accelerated the pace of discovery and lowered the cost so much that scientists pushed on from that single reference genome to sequence the genomes of more than 1,000 individuals in

all their variations. These days, individual patients — and sometimes healthy people, too — can have their personal genomes scanned or fully sequenced. This knowledge about the basic elements of human genomes and their differences, both common and rare, is central to the concept of personalized medicine. It's changing the field of medicine, even though many of us probably haven't noticed any direct evidence of it at the family doctor's office yet.

A 2013 survey by GfK, a global consumer research firm, found that just 27 percent of people interviewed had heard the term "personalized medicine." Of those, only 4 percent understood what the phrase most often implies: "medicine based on genomic makeup."

AN OUNCE OF PREVENTION

There have been recent, high-profile examples: Angelina Jolie made headlines with a proactive double mastectomy last year after tests showed she carried BRCA1, the same genetic marker for breast cancer that her mother, who died from the disease, carried. The National Cancer Institute puts the risk of breast cancer for those carrying a BRCA1 mutation at 65 percent and the risk of ovarian cancer at 39 percent.

While it's important to remember that genes are not destiny, they do provide information that can lead us to make more informed decisions about our health and healthcare, and, as in Jolie's case, that can change the future.

If you get sick, knowing your genome or the molecular basis of your disease can be an important piece of evidence for doctors seeking the most favorable treatment plan for you. In the case of cancer, genetic tests could lead to successful drug treatment rather than radical surgery. For instance, melanoma can be BRAF positive, meaning the tumor has a specific gene mutation that sets it apart from other melanomas. Your lung cancer can be EGFR or ALK positive. Your colon tumor may be KRAS positive.

Increasingly, doctors will scan not just single genes or a handful, but also complete genomes. The challenge then will be figuring out what it all means and what to do next.

"While personalized medicine is escalating and becoming more common, it's still in its infancy, and there are not yet enough products on the market that have penetrated the consciousness of the average patient," says Edward Abrahams, president of the Washington, D.C.-based Personalized Medicine Coalition. "Patients are not yet asking the question 'Is this therapy going to work for me?' I look forward to the day patients do ask that question."

If you find the idea of personalized medicine more than a little overwhelming, you're not alone. It isn't easy to turn an approach to healthcare on its head.

"I don't think anybody disagrees with the fact that we [patients] are different and we respond differently. But it's hard to make changes," Abrahams says. "You want to see evidence before you're willing to move away from one-size-fits-all traditional medicine. To change it, you have to show that what you're promising is an improvement."

TESTING, TESTING

While more evidence about the promise of personalized medicine is certainly called for, individual stories are already pointing the way. In 2005, Stephanie Haney, now 45, had a pain on her right side that wouldn't go away. It hurt when she coughed or sneezed. She was pregnant, so she didn't investigate the cause, assuming perhaps she'd broken a rib.

Two years later, she was diagnosed with stage 4 lung cancer.

After undergoing chemotherapy, Haney began taking Tarceva (erlotinib) in 2008. But three years later, the drug was no longer keeping the tumors at bay. Prompted by friends and an insistent doctor, she had genetic testing on her tumors, which showed they were ALK (anaplastic lymphoma kinase) positive. This gave her doctor a major clue as to which drugs were most likely to work (or not). Haney was able to start taking Xalkori (crizotinib), designed specifically for ALK-positive lung cancer tumors. She joined a clinical trial for Xalkori in Philadelphia, two and a half hours away. Three years later, her tumors were barely visible.

Haney's journey is emblematic of the ever-growing personalized medicine matrix, wherein spreadsheets will be filled with biomarkers for diseases, if not whole genome sequences, and treatments will be fast-tracked (like her Xalkori) for approval based on clinical trials designed for those who have certain biomarkers or genes.

Researchers have discovered more than 1,800 disease genes

"PATIENTS ARE NOT YET ASKING THE QUESTION 'IS THIS THERAPY GOING TO WORK FOR ME?' I LOOK FORWARD TO THE DAY PATIENTS DO ASK THAT QUESTION."

since the Human Genome Project's completion. There are now more than 2,000 genetic tests for human conditions and 350 biotechnology-based products currently in clinical trials.

Lung cancer treatment is one of the most advanced areas in terms of a personalized medicine approach, with several drugs approved by the FDA or in clinical trials for different lung cancer biomarkers. Unfortunately, but not unexpectedly, Haney found out last October that the cancer had moved to her brain, one of several places lung cancer is prone to migrate. Because Xalkori will not break the blood-brain barrier, she just started another trial drug, LDK378, to treat the brain tumor.

CALEB NOLAN, 8, IS ON TWO BASKETBALL teams. Diagnosed with cystic fibrosis when he was 3 weeks old, he has spent much of his childhood in hospitals, taking many rounds of medicines each day. Like other cystic fibrosis patients, Caleb has a mutation in a gene called CFTR that causes mucus to clog the lungs and obstruct the pancreas so the body can't absorb food.

Caleb was on enzymes that allowed him to live with his condition, but life was difficult, and activities such as sports were limited.

With Kalydeco, "Instead of the mucus building up, the medicine is thinning it," Shane says. "Now his body naturally does this. The medicine is preventing damage from the CF. Caleb hasn't been in the hospital since he's been on it [almost two years]. Usually, once kids reach their late teens or early 20s, they have to get a lung transplant. This should prevent that."

The average lifespan of a person with cystic fibrosis is 37. Now, "Caleb could die of old age instead of CF," Shane says.

WHO PAYS FOR THIS?

Caleb was lucky. His insurance paid for Kalydeco from the start. Jolie probably barely registered the $3,000 price tag on her genetic screening, although she did point out in a *New York Times* opinion piece that the price could be an obstacle for many.

When the FDA clearly ties a genetic mutation to a specific drug or treatment, insurers generally do cover the testing and treatment, whatever they pay for works better than what we're used to paying for. But that's a barrier to innovation."

When it comes to whole genome sequences, the uncertainties about outcomes are that much greater, but sequencing is getting cheaper all the time. In January, Illumina, a genetic-sequencing company based in San Diego, announced it had a new system that brought the cost for sequencing a human genome down to less than $1,000. (That's cheaper than Jolie's single BRCA1 test.) This doesn't put a sequencer in your local doctor's office — nor does it cover the cost of interpreting those results — but it does make it feasible for clinicians and researchers to gather the evidence needed to push personalized medicine over the tipping point.

The D.C.-based Personalized Medicine Coalition has made defining levels of evidence that will be acceptable to the Centers for Medicare & Medicaid Services and private insurers a top priority. If a treatment or drug is outside medical guidelines, reimbursement is unlikely.

"Medicine needs to be evidence-based," Abrahams says. "Reimbursement is right up there with research in terms of priorities."

WHO OWNS THE DATA?

With all this data come new questions and ethical and practical challenges about privacy, access, ownership, and more. In many cases, research or clinical trial participants aren't given their results at all. Companies like Myriad Genetics, the primary provider in the United States of clinical BRCA1 testing, have returned individual results to doctors and

IT'S TIME TO GET TO KNOW PERSONALIZED MEDICINE

According to a May 2013 study by GfK, a global consumer research firm, there was little familiarity with the term "personalized medicine" in the general population.

27%
OUT OF 602 RESPONDENTS, ONLY 27 PERCENT HAD HEARD THE TERM "PERSONALIZED MEDICINE"

8%
OF THOSE, 8 PERCENT CONSIDERED THEMSELVES "VERY KNOWLEDGEABLE"

4%
ONLY 4 PERCENT WERE ABLE TO ACCURATELY DEFINE THE TERM

There are many different mutations of CFTR that lead to cystic fibrosis. Fortunately for Caleb, he has a mutation, G551D, found in 4 to 5 percent of cystic fibrosis patients, for which there is a treatment. Caleb is now on Kalydeco (ivacaftor), a genetically targeted treatment approved by the FDA in 2012 and the first such drug that treats an underlying cause of cystic fibrosis.

Shane Nolan, Caleb's father and a UPS driver, will never forget delivering his son's first shipment to their house. Before Kalydeco, says Bruce Quinn, senior health policy advisor at Foley Hoag LLP. If you have a family history that calls for it, insurance will pay for BRCA1 testing (in fact, the Affordable Care Act requires it). Where there is no such specific tie, insurance carriers have a judgment call to make.

Patients with cancer are more likely to have their tests covered. "They have an interest in this because they don't want to prescribe drugs that won't work," Abrahams says. "Insurance companies rightly want to see evidence that

patients, of course, but Myriad has kept the bulk of its data as a trade secret.

Weiss, of Harvard Medical School, says patients are and always will be the rightful owners of their personal genetic data.

"This is confidential patient data," he says. "It can be used for medical research, but it's highly unlikely that your identity will be disclosed to some commercial third party in any identifiable way. Academic medical centers may partner with pharmaceutical companies, using their genomic data, but will do it in an anonymous way and only if the patient consents. The patient is going to be in control of what they do here, as they should be."

Laws such as HIPPA (Health Insurance Portability and Accountability Act) and parts of the Affordable Care Act protect the privacy of personal health information. The passage of the Genetic Information Nondiscrimination Act (GINA) in 2008 was considered a major win, too, as it bars employers and health insurers from using genetic information or family history. Still, many people worry about such personal and sensitive information being out there. And genomic data is at the core of personalized medicine.

"You can't do personalized medicine when it comes to genomics without electronic medical records and without the ability to deliver genomic content to providers at their desktop," Weiss says. "We're not really talking about the doctor-patient relationship here. We're talking about the mechanics of how you deliver huge amounts of data to clinicians in the office and at the bedside."

Medicine is getting there slowly but surely. The Obama administration began moving our healthcare system toward electronic records in the summer of 2009. Now more than 50 percent of medical records are available in electronic form.

"We need to get to 100 percent, and just having an electronic medical record isn't enough," Weiss says. "We still have to have software focused on the genomic content delivery to the caregiver."

Ideally, doctors could tap into a single, large database filled with anonymous genetic information — biomarkers tied to patient demographics tied to specific drugs and treatments — to help doctors make decisions about each individual's medical path. But getting there is sure to be a long and bumpy ride, with plenty of detours along the way.

For Daryl Pritchard, director of policy research at the National Pharmaceutical Council, the end game is clear: "The use of that information — whether by a company or by a group of doctors or a provider group — is ultimately going to be advantageous to treating the condition in question going forward. These things will work."

TALK TO YOUR DOCTOR

Starting with a good family history is a smart and simple way to begin a personalized medicine discussion with your doctor, says Geoffrey Ginsburg, director of the Center for Personalized and Precision Medicine at Duke University Medical Center, although it doesn't happen often enough. (Ginsburg is also editor-at-large of *Genome* magazine.) While you're at it, he suggests asking about whether any genetic tests are useful for regulating a dose of a drug, an approach known as pharmacogenomics.

Abrahams recommends asking your doctor the following question: "Do you have the expectation that this drug will work for *me*?"

According to Randy Burkholder, the vice president of policy and research for Pharmaceutical Research and Manufacturers of America (PhRMA), a Washington, D.C.-based trade group representing American biopharmaceutical and biotechnology companies, the most important thing is not being afraid to ask your doctor questions.

"It can be a hard thing to do sometimes, especially when you're seeing a diagnosis," he says. "Asking questions allows you to work with your doctor. The volume of information we can know is so much greater now. Doctors are doing a great job, but they can't be expected to know everything for every patient. As a patient, you shouldn't feel like you're imposing. You should feel like you're helping."

WHERE IS PERSONALIZED MEDICINE HELPING MOST?

Personalized medicine's greatest strides have been in cancer. Consider these statistics on the percent of tumors containing genetic mutations that could be targeted by drugs, as reported by the *Wall Street Journal* in 2011:

- Melanoma: 73 percent
- Thyroid: 56 percent
- Colorectal: 51 percent
- Lung and pancreatic: 41 percent
- Breast: 32 percent

"Cancer is a genetic disease," Ginsburg says. "In many ways, it is the poster child for a disease that has used personalized medicine

"PERSONALIZED MEDICINE IN THE AGE OF GENOMICS MEANS WE'RE LIVING IN DYNAMIC TIMES. THE BIG QUESTION RIGHT NOW IS 'HOW DO WE TAKE ALL THIS NEW INFORMATION WE'RE GATHERING AND USE IT FOR THE BENEFIT OF THE PATIENT?'"

strategies. It has used them in everything from risk assessment in healthy people — from screening, diagnosis, and prognosis — to selecting therapies based on genetics and the biology of the tumor."

HIV/AIDS is another area where the principles of personalized medicine have made great progress. "The virus mutates differently in each patient," Abrahams says. "Now we can understand the viral load and analyze it, then prescribe the right cocktail of medicine to treat it. This is the progress we've seen taking AIDS from a death sentence to a chronic condition. But that's understanding the virus, not the person."

Other diseases are clearly moving toward more comprehensive personalized medicine strategies, too, including heart disease, rheumatoid arthritis, multiple sclerosis, and infectious diseases. "Also, rare disease diagnosis is now becoming more amenable to personalized medicine strategies through genomics," Ginsburg says.

THE FUTURE OF PERSONALIZED MEDICINE

Abrahams is optimistic about the progress now being made, particularly when it comes to complex chronic diseases.

"At some point, and I don't know whether that will be 10 or 15 years from now, we will reach that tipping point where all medicines are linked to diagnostics, and we'll move out of the one-size-fits-all paradigm," he says. "If we have good answers today with the one-size-fits-all model, I don't think that will change. But most patients are unaware of the limits of our medical knowledge."

Once the evidence is in, many pieces will need to fall into place before personalized medicine becomes mainstream. Payment systems must be flexible enough to account for individual treatment plans based on genetics and other indicators. Regulatory guidelines must adapt to the idea that genetic diagnostics and targeted drugs go together in a treatment plan. Medical schools must include personalized medicine in their curricula. Patient interest and demand are essential, too.

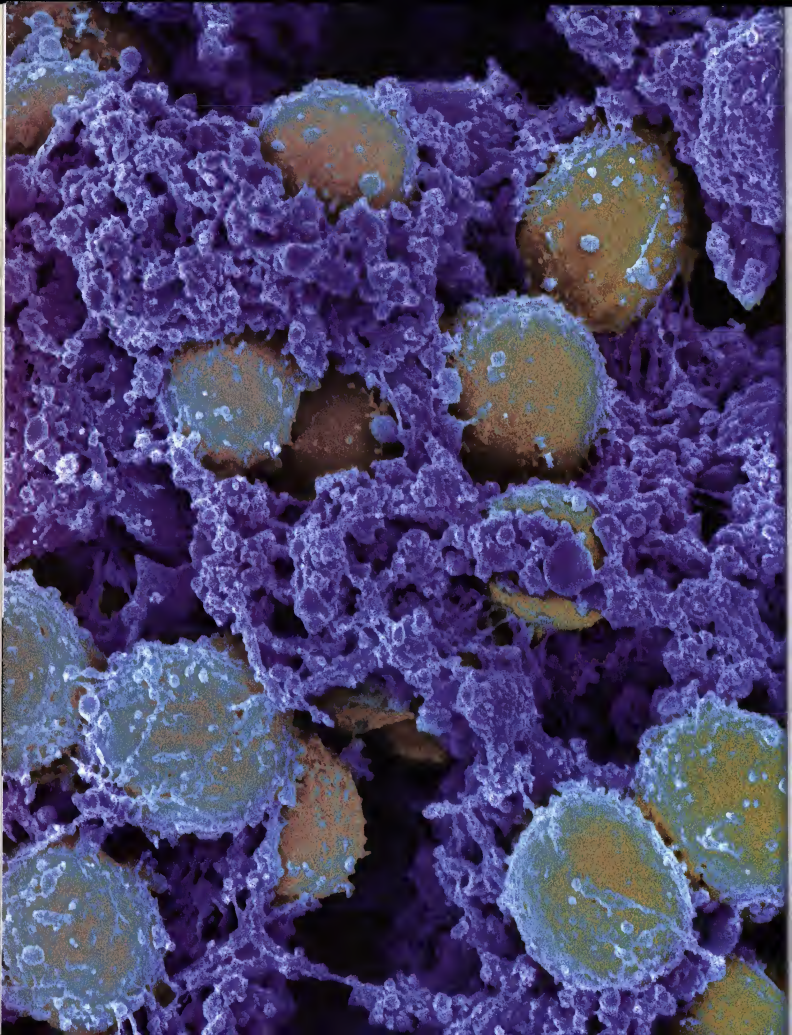
While some patients may be seeing the impact of personalized medicine in some corners already, patient outcomes with today's medicine show plenty of room for improvement. Consider patients with depression, 38 percent of whom do not respond to the first drug they are prescribed. Or patients with asthma, of whom 40 percent do not respond to the most commonly prescribed drugs. Or type 2 diabetes (43 percent), arthritis (50 percent), and Alzheimer's disease (70 percent).

Education will be key. Knowing that tailored treatments are or may be available for various diseases is half the battle. Abrahams looks forward to the day when both patients and doctors will advocate for personalized medicine.

"One day, patients will say, 'I'm not an average patient. I am who I am. You need to understand who I am before you prescribe whatever treatment you plan to prescribe,'" he says. "When that day comes, we'll no longer [have to] talk about 'personalized medicine.'"

We'll know we've arrived when personalized and genomic medicine simply *is* medicine.

Kendall Morgan contributed to this report.



CHANGE YOUR MICROBIOME, CHANGE YOURSELF

Growing research into the human microbiome — also known as the "other human genome" — shows that the trillions of tiny bugs that live in your gut could hold the keys to new treatments for conditions ranging from obesity and Crohn's disease to allergies and asthma. By Kendall K. Morgan

IF YOU THINK YOU'RE ONLY HUMAN, YOU'D BETTER THINK AGAIN.

Single-celled bacteria living in and on our bodies outnumber human cells by at least 3 to 1 — and perhaps as much as 10 to 1. The latest estimates from the American Academy of Microbiology put our bodies at 37 trillion human cells and our microbiomes — as those bugs are collectively called — at 100 trillion. Yes, that's right, our skin and guts, mouths and noses, along with every other body surface, are home to 100,000,000,000,000 microscopic bugs. The typical human microbiome is said to represent about 1,000 different species, with wide variation from one person to the next in exactly which species. If it's still hard to fathom just how big a single microbiome is, consider this: That same report says those microbes, each vanishingly small and seemingly weightless on its own, add up to something like 2.5 pounds.

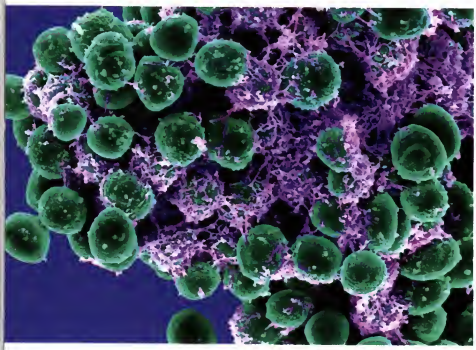
If these statistics have you reaching for the hand sanitizer, slow down. The vast majority of these bugs are no threat at all. Quite the opposite, in fact. Many of them are our best friends and allies in myriad surprising ways that scientists are only now beginning to sort out. And to think that with all of those antibiotics and disinfectants we've been waging an all-out war. We really haven't known microbes (or ourselves, for that matter) at all.

"We've had this perception of microbes as germs, as pathogens, as disease-bearing organisms," says Lita Proctor, a scientist at the National Human Genome Research Institute and program director of the Human Microbiome Project. "Much of the scientific literature for decades and decades has been completely focused on pathogens, and that has also framed our point of view about microbes. But it has become clear that the vast majority of microbes we come in contact with on a daily basis are not pathogenic. They are either benign and couldn't care less that there is a human nearby or they actually provide a benefit."

Bacteria play essential roles in the development of our immune systems as newborn babies are colonized at birth and subsequently by microbes from mom and the environment. Once established, those microbes, and particularly those that fit our cells like a lock and key, provide us with energy sources and vitamins humans can't make on their own. They produce ingredients that act as anti-inflammatories and send signals to our brain. "Good" microbes help us fend off the "bad" ones. We really can't live without them.

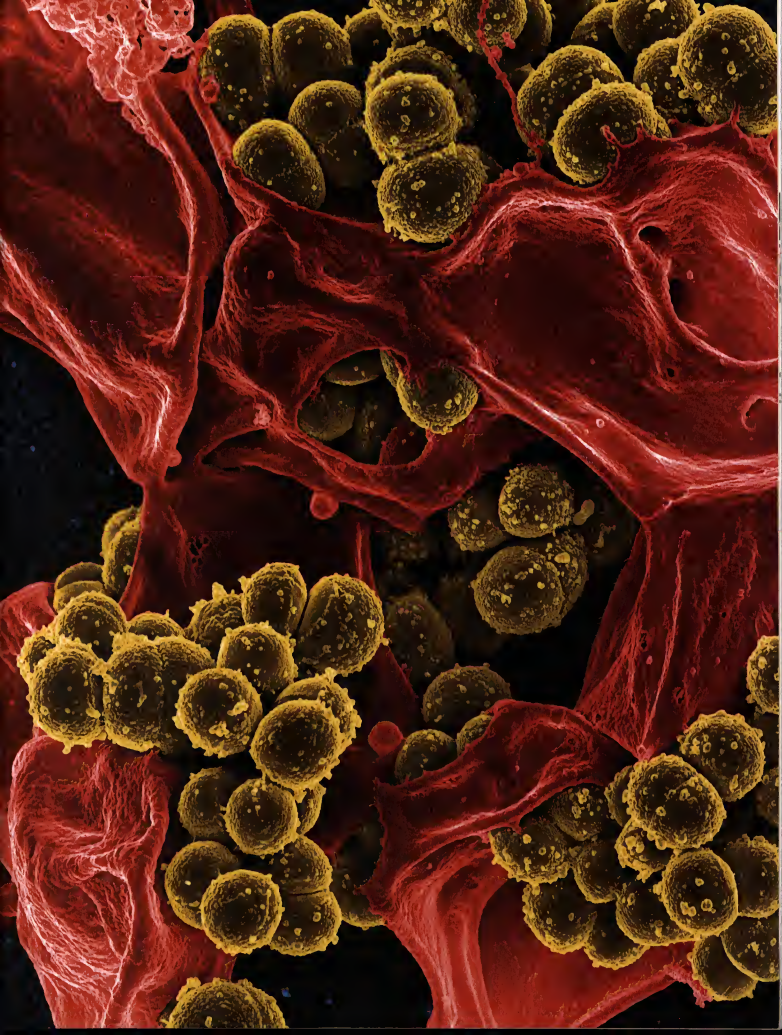
THE OTHER HUMAN GENOME

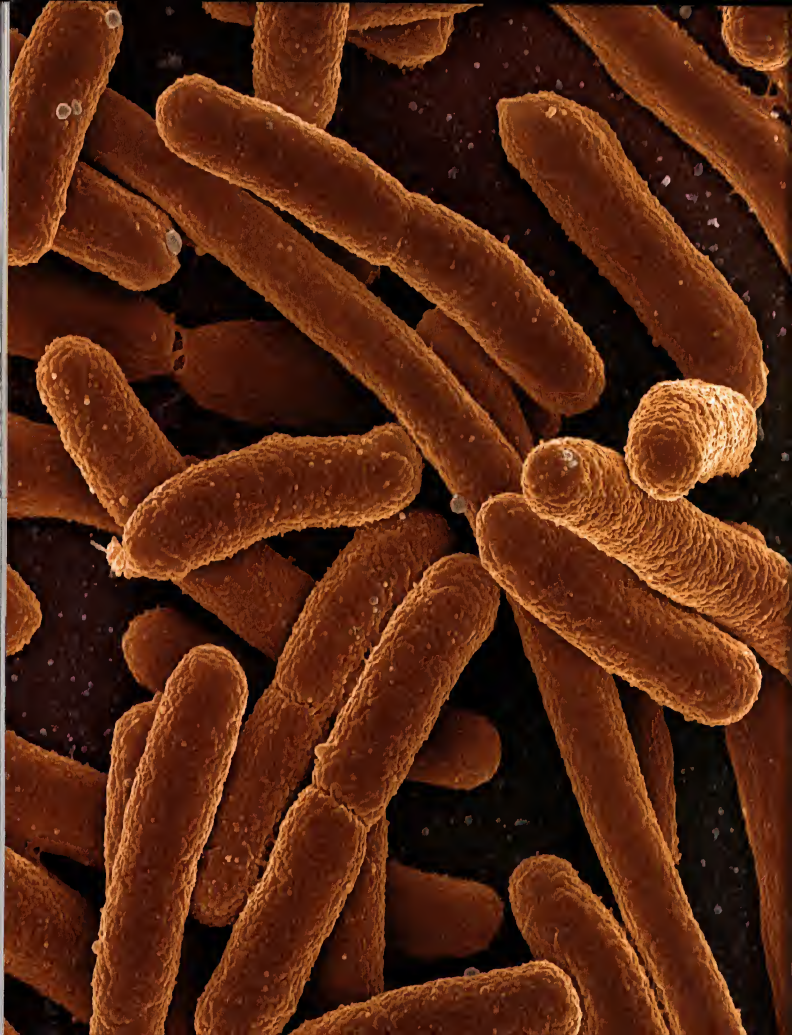
Despite their importance and value, all of these microbes had gone mostly unrecognized, especially in the biomedical field. That began to change substantially in 2007 when the National Institutes of Health launched the Human Microbiome Project, an effort to catalog the microorganisms living in and on healthy human bodies. It was in some ways a follow-up to the Human Genome Project. Scientists would apply rapidly improving DNA sequencing technologies to define what some like to consider the "other human genome"



An estimated 100 trillion microscopic bugs are living in and on your body right now. The good news is that many of those microbes are there to help, not hurt.

COURTESY: NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES





– the human microbiome — via samples taken from hundreds of healthy people and many parts of their bodies: behind the ear, the inner elbow, the lower intestine, and the mouth. The object of study was literally right under our noses, but it was still so foreign that NIH Director Francis Collins has likened the researchers who carried out the work to "15th-century explorers describing the outline of a new continent."

The result is the first comprehensive picture of what a normal human microbiome looks like, at least in these modern times. "We have defined the boundaries of normal microbial variation in humans," said James Anderson, director of the NIH Division of Program Coordination, Planning, and Strategic Initiatives, in the release issued by the NIH as the first big batch of Human Microbiome Project studies were published last year. "Now we have a very good idea of what is normal for a healthy Western population and are beginning to learn how changes in the microbiome correlate with physiology and disease."

A VERITABLE EXPLOSION

Since then, there has been an avalanche of new studies connecting the microbiome to health on the one hand and disease on the other. A disrupted microbiome, driven perhaps by the overuse of antibiotics combined with an overprocessed food supply, is now a suspected contributor to the obesity epidemic. Those disruptions often arise from the very first days of life as babies delivered by C-section miss their first inoculation with healthy bacteria found in their mothers' vaginas. Formula-fed babies also show significant differences in their microbiomes compared to those who are breastfed.

A study reported in *Science* found that differences in the microbiome might help to explain instances in which one individual in a pair of twins is obese while the other is not. Microbiome samples taken from obese twins and delivered to mice led the animals to gain weight in a way that the microbiomes of their leaner siblings simply did not. And a comparable study of mice and twins from Malawi showed that differences in the microbial composition of the gut could explain how two children in the same family sometimes differ so markedly when it comes to malnutrition, too.

If changes to our microbiomes might be a cause of obesity, perhaps they can be a cure for it, too. The gut microbiome apparently undergoes drastic change after gastric bypass surgery, and it gets better: Overweight mice given a "post-surgery" microbiome (but no surgery) lose weight, too.

There are other observations that may seem even less obvious. Changes in the intestinal bacteria may explain why HIV patients—even those who do well with treatment — sometimes still suffer from chronic and ultimately life-threatening diseases. Less diverse gut microbiomes have been linked to the risk of some cancers. Signals produced by the gut microbiome influence blood pressure. The microbiome plays a role in the way our bodies metabolize and respond to some prescription drugs.

In December, a study in mice added to evidence that the microbiome can influence the brain. Animals susceptible to autism-like symptoms as a result of infections suffered by their mothers during pregnancy also showed changes in their microbiomes. When researchers at the California Institute of Technology treated the mice with healthy gut bacteria, some of the animals' abnormal behaviors and anxiety went away.

"Instead of declaring war, we need to think in the context of ecosystems that make up our bodies. Figuring out how to encourage good microbes while eliminating the bad will be of increasing importance."

Changes in the microbiome have been linked to obesity, inflammatory bowel diseases, allergies, and asthma, which means the key to treating such disorders could be right under our noses.

"The microbiome is actually our first line of defense. When you kill it off with antibiotics, you really are doing your own system a disservice."

Even our family dogs are in on it. Another study just found that the dust in dog-friendly homes protects against allergies and asthma through changes (you guessed it) in the gut microbiome. Young mice fed on doggy dust didn't react much to cockroach allergen compared with animals fed pet-free dust or none at all. While much of the attention is on the gut, similar things are happening on our skin.

THE MODERN AGE

There is reason to think that the Western microbiome has changed in the last century and not necessarily for the better. A study led by researchers at the University of Oklahoma of microbiome samples taken from ancient people — including Otzi the Iceman and a soldier frozen for decades on a glacier — show that our guts used to look more like those of other primates and rural people in less developed countries. These relatively recent microbiome changes might help to explain the rise in certain kinds of diseases even as modern medicine has enabled us to overcome so many others.

"If you look at a lot of the disease issues of the 20th and 21st century, a lot of them have to do with nutrition and autoimmune processes," says David Suskind, a pediatrician and gastroenterologist at Seattle Children's Hospital. "We don't have a definitive cause yet, but as we look at the new science being done, we see a lot of connections to the microbiome and dysbiosis," meaning microbial imbalances.

Suskind rattles off a list including arthritis, gum disease, obesity, and cardiovascular disease. His primary interest, though, is inflammatory bowel diseases (IBD) — Crohn's disease and ulcerative colitis — and their symptoms, including persistent and painful diarrhea. IBD has been considered an autoimmune disease and treated as such with immunosuppressant drugs. But there are reasons to suspect there's more to it than that.

"IBD is considered an autoimmune process attacking the gastrointestinal tract and other organs," Suskind says. "But humans have been around for millennia, and IBD is a relatively new disorder."

Doctors started to notice IBD symptoms about 40 to 50 years ago, he says. Since then, the incidence has only risen. There is evidence to connect IBD to immunity-related genes, but what's the trigger? Suskind says the evidence is pointing to the microbiome. What would happen if, instead of crippling their immune systems, you gave patients with IBD a new and improved set of bugs?

POWERFUL POOP

It turns out there is a relatively simple if slightly unappetizing way to do that. The method is called a fecal transplant, and it's exactly what it sounds like. Doctors infuse patients with slurries of fecal matter taken from healthy people, delivered either to the intestine by enema or the stomach through a nasogastric tube. It's the quickest and easiest way to replace a microbiome, even if the bacteria and other ingredients going in aren't entirely clear.

In an example that remains the poster child for the power of the microbiome (and of poop), researchers in the Netherlands published a report early last year in the *New England Journal of Medicine* showing that an infusion of donor feces can be a miracle cure for patients with recurrent and miserable *Clostridium difficile* infections, whose symptoms include diarrhea and severe abdominal pain. The results were so clear, in fact, that the study had to be stopped early after an interim analysis showed 81 percent resolution of symptoms in patients after a single infusion of stool. By comparison, patients given standard antibiotic treatment had little more than a 30 percent chance of recovery.

"That was the reason we had to stop," says Josbert Keller of the University of Amsterdam, who led the trial. "We could not continue randomizing patients with very low a priori chance they would be cured by vancomycin. It was not ethical to prescribe the standard therapy anymore."

That's not to say that antibiotics are never the answer for *C. difficile* infection. In most patients, vancomycin will do. But once a patient suffers repeated bouts of the infection, Keller says, they really deserve a fecal transplant.

Suskind and his colleagues have recently completed an FDA-approved pilot study in kids with Crohn's disease or ulcerative colitis as a first step to finding out if the same might hold true in IBD. They treated kids with fecal samples delivered by nasogastric tube, a measure to ensure the microbial cells would reach the whole of the GI tract. While the results have yet to be submitted for publication, Suskind says they have evidence, in Crohn's at least, that a fecal transplant may put patients into remission.

"If we can change the microbiome, we may be able to improve symptoms and lab response," he says. "It has the potential to really shift the paradigm of treatment. It's preliminary and it's not a cure-all, but I truly do think this will have a real impact on IBD therapy."

It's worth noting that fecal transplants aren't for everyone, and they don't come without risk either. After all, they include undefined microbes and viruses, and experts emphasize the importance of careful screening. For those who really do stand to benefit from a borrowed microbiome, eventually there are likely to be simpler ways to obtain fecal samples and receive them in more standardized and appealing manners. A nonprofit called OpenBiome recently launched in the United States as a source for screened fecal samples, with the goal of making the transplants faster and easier for patients and their doctors, and a Toronto hospital reportedly opened the first fecal self-banking system. In even better news, researchers in Canada have some evidence that a fecal transplant pill can knock out *C. difficile* infections, too.

"If the pills work, that's the way we should do it," Keller says. When scientists know more, it might be possible to fill those pills with precise bacterial mixtures in place of poop. There is plenty of promise in probiotics, even if the FDA doesn't know quite how to regulate and test them just yet. Still, for now, no one really knows what distinguishes a good microbiome from a bad one.

GO WITH YOUR GUT

What is clear is that most microbes aren't out to get you.

"I think we are coming around to the view that most microbes are indeed beneficial," says Rob Knight of the University of Colorado Boulder. "Instead of declaring war, we need to think in the context of ecosystems that make up our bodies. Figuring out how to encourage good microbes while eliminating the bad will be of increasing importance."

Knight is one of the leaders of a crowdfunded and crowdsourced study called American Gut, which aims to move the science of the human microbiome ahead by allowing anyone to submit his or her sample for analysis at a $99 fee. They'll take samples from family members, too, dogs and cats included. (In case you were wondering, they don't recommend pet alligator samples. "It's just hard to get the fecal sample safely.")

Knight says it's still very early in terms of what people can learn beyond curiosity by participating in American Gut, and they are certainly not providing a medical test. "The main aim is really to democratize the technology and make it accessible for the first time to a wide audience," he says.

It's clearly working. They've received more than 8,000 samples and raised almost $340,000 on Indiegogo. Eventually, as the data come in and become integrated with other clinical findings, it may become possible to learn much more about what your unique microbial makeup might mean for health and disease — and perhaps also how to change it.

Right now what American Gut offers is a way for people to take a peek at their personal microbiome and to see how they fit with their larger human community. Knight says they will soon add a new "challenge feature" based on the recent findings of Harvard scientists that sudden and extreme dietary shifts — to either a vegetarian or wholly meat-based diet — can alter the microbiome in a matter of days.

DOWN AND DIRTY

It's likely the microbiome is responsible in part for many things we already know about healthy living: why it's good to eat leafy greens and best to leave the french fries alone, for instance. Other lessons might be harder to swallow, depending on your attitudes about hygiene.

Knight lets his toddler daughter eat off the floor, get dirty outside, and interact with livestock — all things that support a diversity of microbes and perhaps lower risk of infection and autoimmune disease. (Full disclosure: These practices also come as good news for me.) As for the NIH's Proctor, her best advice for now is to stay tuned and lay off the antibiotics, which she likens to sledgehammers.

"They kill off not only germs but also the microbiome, leaving you vulnerable to invasion by other microbes," she says. "The microbiome is actually our first line of defense. When you kill it off with antibiotics, you really are doing your own system a disservice."


welcome
to you
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WHY IS THIS $99 HOME DNA KIT CAUSING SUCH AN UPROAR?

23andMe says it can provide you with valuable health information about your genes. The FDA says prove it.
What the consumer genetic testing battle means for you.

BY JOSEPH GUINTO

WOULO YOU GIVE SOMEONE YOU LOVE A SMALL PLASTIC VIAL FOR HER BIRTHOAY ANO ASK HER TO SPIT INTO IT?

Rob Abrams did. His wife, Caitlin, couldn't have been happier. She liked it so much she gave Rob the same thing for Christmas. "It was," Caitlin says, "the most nerdy gift I have ever given and received."

The package — a small tube, removable cap, and sealable spit funnel — was a genetic testing kit from California company 23andMe. The Abramses spent $299 on each kit in 2011. Once the couple mailed in their tubes, 23andMe tested their saliva for hundreds of genetic markers. The markers pointed toward clinically useless but nevertheless interesting ancestral information (look, Caitlin had 2.9 percent Neanderthal DNA!). They also pointed toward dozens of potential health risks. By comparing some of the couple's DNA to a database of genetic indicators, the company said it could tell them whether they were at increased risk for a range of diseases, including Alzheimer's disease, breast or prostate cancer, type 2 diabetes, hypertension, heroin addiction, and amyotrophic lateral sclerosis.

And celiac disease, which Caitlin already knew she had. "I was most interested in possible inherited diseases," she says. "I'd been diagnosed with celiac disease only a year or two prior, and given that my husband and I planned to have children, I thought it might be helpful to see if I was genetically predisposed to it. Since we know that my celiac disease is based in genetics, we felt that we should speak to a doctor about how to avoid exposing our baby to gluten too early and raising his or her risk of presenting the disease at a later date."

That's exactly what the Abramses, who live in Santa Fe, New Mexico, did after Caitlin became pregnant last year. And that's exactly the kind of thing that helped make 23andMe so popular. The company's Saliva Collection Kit and Personal Genome Service promised consumers direct access to their own genetic data as a first step to helping them delay, diminish, or even prevent development of the kinds of serious medical conditions that might otherwise cause them a lifetime of discomfort or distress.

Its most revolutionary revision: It did so without requiring customers to first visit a healthcare provider. And it worked. As of last year, when the price of 23andMe's testing kit decreased to just $99, the company had signed up 400,000 customers. (That number has now climbed to about 500,000.) It was also the only company in the market providing health-related genetic testing directly to consumers. As such, it became a media darling. *Time* named the company's testing kit the "invention of the year." *Bloomberg Businessweek* said the kit was part of the "next billion-dollar opportunity in healthcare." And just as 23andMe CEO Anne Wojcicki began making the rounds on *Today* and *CBS This Morning*, *Fast Company* magazine named her "America's Most Daring CEO."

One organization that wasn't applauding: the U.S. Food and Drug

Below: If you take 23andMe's spit test today, you will receive a report on the likely migration patterns of your ancestors. What you will not receive is any information on potential health risks.
Right: By analyzing hundreds of genetic markers, 23andMe says it can tell customers whether they are at increased risk for diseases ranging from Alzheimer's to hypertension. The FDA is not convinced that's true.

COURTESY 23ANDME

Administration. In November 2013, the FDA told the company it had to shut down the service. As of press time in April, you could still take 23andMe's spit test for $99, but when you receive the results, you'll only be told about the likely migration patterns of your ancestors. There will be no interpretation about what your genes may mean for your predisposition for celiac disease or Alzheimer's or cancer or ALS or whether your yet-to-be-conceived child may have blue eyes.

That's because the FDA has deemed 23andMe's "nerdy" product to be a medical device that the agency can regulate. It is the FDA's mission to make sure that medical devices are safe and accurate, and the agency was concerned that 23andMe's spit test had not been proven to be either. FDA spokeswoman Susan Laine told *Genome* that the agency could not elaborate on its dealings with 23andMe, saying, "We cannot comment or confirm communication between FDA and the company at this time." But in a letter sent to 23andMe on November 22, 2013, the FDA's Alberto Gutierrez said 23andMe's test could raise serious concerns "if test results are not adequately understood by patients or if incorrect test results are reported."

The FDA has raised concerns about genetic testing for the masses before. In 2010, San Diego-based Pathway Genomics scuttled plans to sell a genetic testing kit in Walgreens stores after the FDA balked. Since then, the company has required customers to have a physician order the test for them. The FDA says its aim is simply to protect consumers from misinformation about their health, or from having access to information they won't fully understand. But others see these moves by the FDA as a rebuke of the current movement toward patient empowerment and the democratization of healthcare — a rebuke that may grow in scope this year. Or, as Nick Gillespie, editor of libertarian website Reason.com, bluntly put it: "When it comes to learning about your own [damn] genes, the FDA doesn't think you can handle the truth."

But the truth about the FDA's actions regarding 23andMe may simply be about protecting consumers. The government has been suggesting for years that something is suspect in the direct-to-consumer genetics information provided by companies like 23andMe. In 2006, the Government Accountability Office, a congressionally funded watchdog, investigated four companies that were testing DNA and offering personalized nutrition. The GAO said it believed all of the companies were misleading consumers by basing their guidance on medically unproven test results. Subsequently, a handful of other government agencies, including the Federal Trade Commission and the FDA, issued warnings to consumers about the reliability of the tests.

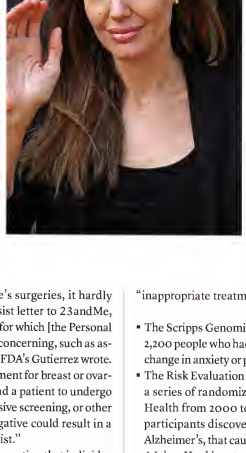
"The test results we received are misleading and of little or no practical use to consumers."

—Gregory Kutz, an investigator with the Government Accountability Office

The GAO and the FDA are not alone in their concerns. Some medical experts believe the information 23andMe gave consumers was incomplete at best and dangerous at worst. But there are others who believe that giving consumers easier access to genetic information, whether clinically proven or not, will help the long-term health of many individuals and help build a bigger, better database of genetic research. Given the differences of opinion and with 23andMe (as of press time) hamstrung by FDA regulations, it's worth asking: How much information can you now easily obtain about your genetic makeup? And, now that consumers have shown they want to know more about their genes, how will the FDA respond if other entrepreneurs find ways to leverage new technologies that might give consumers that information?

ON JULY 9, 2013, *US WEEKLY* BREATHLESSLY REPORTED that Angelina Jolie was seen in Hawaii "rocking a plunging neckline." The report, accompanied by photos from the event, went on: "Wearing a low-cut camisole and black pants, Jolie revealed her stunning figure and still-ample cleavage." That an actress once named the "sexiest woman alive" would wear a camisole in Hawaii, much less look attractive in it, would hardly seem like breaking news. But this was the first hint of décolletage Jolie had shown in public since she announced, two months earlier, that she'd undergone a double mastectomy and breast-reconstruction surgery.

That announcement did more than put the paparazzi on alert; it imprinted the names of two genes — BRCA1 and BRCA2 — onto the consciousness of thousands of American women. Commonly pronounced "brak-ah one" and "brak-ah two," these are genes that, when inherited in mutated form, can cause breast or ovarian cancer. According to the National Cancer Institute, about 12 percent of women may develop breast cancer at some point in their life. But 55 to 65 percent of women with the BRCA1 mutation, and 45 percent of women with the BRCA2 mutation, will develop breast cancer by the time they turn 70. Jolie had a mutation in both genes. Genetic counselors told Jolie that her BRCA mutations, combined with her family history, gave her an 87 percent chance of developing breast cancer.



By now, none of those stats is breaking news, either. According to a Harris Interactive/HealthDay poll of 1,100 women conducted just a week after Jolie's photo was snapped by *Us Weekly* in Hawaii, 86 percent had heard of her surgery. Of those, 5 percent said they also planned to consult physicians about whether to have their own double mastectomies or to have their ovaries removed, which Jolie said she also planned to do because of the BRCA mutations. Harris Poll officials say that when you extrapolate that 5 percent of respondents nationwide, it suggests that 6 million women might now be seeking similar advice on ovary or breast removal.

With such a strong public reaction to Jolie's surgeries, it hardly seems coincidental that, in its cease-and-desist letter to 23andMe, the FDA singled out BRCA. "Some of the uses for which [the Personal Genome Service] is intended are particularly concerning, such as assessments for BRCA-related genetic risk," the FDA's Gutierrez wrote. "For instance, if the BRCA-related risk assessment for breast or ovarian cancer reports a false positive, it could lead a patient to undergo prophylactic surgery, chemoprevention, intensive screening, or other morbidity-inducing actions, while a false negative could result in a failure to recognize an actual risk that may exist."

Numerous genetic experts have balked at the notion that individuals can't put the sort of information 23andMe provides in its appropriate context. Among them, Misha Angrist, an assistant professor at the Institute for Genome Sciences & Policy at Duke, has called the FDA's concern that women will seek and obtain potentially unnecessary mastectomies based on 23andMe's test "borderline absurd." And two top experts in the genomics field recently published a joint rebuttal to the FDA's arguments against 23andMe's service. Writing in the journal *Nature*, Robert Green, a genetic researcher at Harvard, and Nita Farahany, a law professor and bioethics expert at Duke, called the FDA's response "unwarranted." Green and Farahany worry that the FDA's actions against 23andMe could "presage similar actions against other consumer health products" like online questionnaires or mobile apps that provide medical guidance based on a user's input, which the FDA has suggested it might also regulate as "medical devices." Still, Green and Farahany do agree with the FDA that 23andMe has yet to validate all of its findings about the health implications found in the genetic variants of its customers, and both also agree that customers might not fully understand the information they are provided about those implications. But they also believe that "the FDA's precautionary approach may pose a greater threat to consumer health than the harms that it seeks to prevent."

As evidence, they pointed to several studies that suggest inexpensive, direct-to-consumer genetic testing does not create distress in most customers, nor does it push them to get "inappropriate treatment." Among those studies:

- The Scripps Genomic Health Initiative study in 2009 found that in 2,200 people who had their genes tested, "there was no measurable change in anxiety or psychological health" once they had the results.
- The Risk Evaluation and Education for Alzheimer's Disease study, a series of randomized trials funded by the National Institutes of Health from 2000 to 2013, found that even though 40 percent of participants discovered they had an increased risk of developing Alzheimer's, that caused them "only modest and transient distress."
- A Johns Hopkins study in 2010 of three genetics-testing companies found that just over 25 percent of respondents shared their results with their physicians in the months immediately after receiving those

JOLIE: GOSBIS

results. It also found that less than 1 percent of participants altered their medication as a result of their genetic testing.

- The Impact of Personal Genomics Study funded by the NIH from 2012 to 2013 found that customers of Pathway Genomics and 23andMe were "on average ... briefly less anxious" after getting their results and that their anxiety didn't increase over the 12-month period following the receipt of their results.

Some of those studies align with Caitlin Abrams' experience. She says her test results caused her and her husband "no anxiety whatsoever."

"According to my 23andMe results, I have a slightly elevated risk of multiple sclerosis," she says. "This wasn't too surprising to me given that I already have several risk factors, but the confirmation was helpful. In my case, I mentioned the results to my doctor, who told me that in the absence of symptoms I couldn't be tested. She also pointed out the specific symptoms so I could be aware of them in the future."

That is an ideal outcome for personal genetic testing. A customer takes a test and finds that some of her genes suggest an increased risk for a chronic medical condition. That customer calmly discusses those results with a doctor who advises her there is no immediate risk and tells her what to be aware of in the future.

But some in the healthcare field worry that if personal genetics testing grows unregulated, it will too often lead individuals to insist on expensive and possibly unnecessary testing to confirm or overturn what their genes have supposedly told them. Count Jennifer Gunter, an OB-GYN practicing in both Canada and the United States, among the concerned. Writing on her blog, she says that when presented with the kinds of results 23andMe had been providing, doctors could be vexed as to whether and when to order follow-up testing. "You can get test results that your medical providers just don't know how to manage," Gunter says. "I was always taught that I shouldn't order a test if I have no idea what to do with the result."

Left: Angelina Jolie's decision to undergo a preventive double mastectomy introduced thousands of women to BRCA1 and BRCA2 — two genes associated with breast and ovarian cancer. In its cease-and-desist letter to 23andMe, the FDA called the company's assessments for BRCA-related genetic risk "particularly concerning."

"Somehow the U.S. government finds it acceptable to store massive amounts of data about its own citizens and those of the rest of the world. But if the same people want to spend their own money to advance genomic medicine and possibly improve their own health in the process, they want to stop them."

GOOGLE WANTS YOU TO KNOW MORE ABOUT YOUR GENES. Or, at least, one of the founders of the search-engine giant seems to have wanted that. 23andMe was founded in 2006, backed with funding from Google. The company's CEO was (and still is) Anne Wojcicki, the now-estranged wife of Google co-founder Sergey Brin. Brin is also a 23andMe user. Through the company's testing in 2008, Brin discovered he had a mutation in a gene called LRRK2, putting him at elevated risk of developing Parkinson's — a disease his mother already has. Since then, Brin has been on an exercise and nutrition plan, hoping to slow down or stop the onset of the disease. He has also donated more than $130 million to Parkinson's research.

Brin and Wojcicki gladly began telling that story four years ago — to *Marie Claire*, to *Bloomberg*, and to *Wired* magazine, which ran a lengthy profile on the notoriously press-shy Brin in July 2010. That same month, the GAO came out with a report about consumer-level genetics-testing companies.

In the GAO investigation, five volunteers purchased 10 tests from four companies, including 23andMe. Each volunteer got highly conflicting results from the tests. One was told that he was both at below-average and above-average risk for prostate cancer and hypertension. Others received disease predictions that were at odds with their actual medical conditions. Testifying before the U.S. House Subcommittee on Oversight and Investigations, Gregory Kutz, a GAO investigator, concluded, "The test results we received are misleading and of little or no practical use to consumers."

You don't have to look hard to find genetic experts who more or less agree about the practicalities of direct-to-consumer genetic testing, even if they support the right of consumers to have those tests available. At one recent Harvard Medical conference for personalized medicine — which was overrun with doctors and researchers in favor of genetic/genomic testing — the test was called "entertainment" to distinguish it from something with clinical utility. Even those with a 23andMe association are cautious. Michael Eisen, a biologist at the University of California at Berkeley who is also on the scientific advisory panel for 23andMe, recently wrote the following on his personal blog: "Looking at your own DNA is really interesting, but it only rarely provides actionable new information. We have an incomplete catalog

of human genetic variation. ... In many cases current, incomplete, data may point to someone having an elevated risk of some disease, when they really have a lower than average risk. ... The data are, at this point in time, very, very messy."

Besides, Eisen points out, 23andMe's tests only provide "SNP genotyping, not whole genome sequencing." That means the 23andMe test identifies genetic markers known as single nucleotide polymorphisms, often referred to as SNPs (called "snips"). SNPs are positions along the DNA chain where people commonly differ from one another. 23andMe's test measures 1 million of these, but there are many other types of genetic variants that aren't measured by these tests. As Robert Klitzman, who heads the master's of bioethics program at Columbia, put it in a recent *Bloomberg* opinion piece, "The problem with these test kits is scientific. Only part of a person's DNA is tested, and scientists are still unsure how to interpret most of the information. ... The test from 23andMe misses many genes that may be involved in a disease."

The FDA has long agreed. In June 2010, the agency informed five direct-to-consumer genetics-testing companies that it intended to regulate their products as medical devices, which would require the companies to prove the products performed as advertised. By May 2013, as Jolie was announcing her BRCA mutations, the only one of those companies still in the business of selling health-related testing kits directly to consumers was 23andMe. But that same month, the company stopped communicating with the FDA about how it intended to prove its product was accurately matching DNA samples with increased or decreased likelihood of acquiring certain diseases. Six months of silence later, in November 2013, the FDA told the company to stop marketing and providing the health-related aspects of its genetic tests. Care to guess whom *Fast Company* magazine lauded on its cover that same month? Right. Wojcicki. *Forbes*, however, had a slightly different take, headlining a story about the FDA's November 22 action to stop 23andMe's tests as "23andStupid." Wrote *Forbes*' Matthew Herper, "This is not the story of a big regulator choosing to squash a small company, but of a company that decided that it didn't have to follow the rules."

But consumers don't always have to follow the FDA's rules. In addition to a report on your likely ancestry, if you order a 23andMe spit kit today, you will receive raw genetic data that has not been spun through the company's database to match your genetic markers with the potential for developing diseases, or with the ability to smell asparagus in your own urine (which, yes, was part of the test). But you could take that raw data to an outfit like Promethease. Developed in 2006 by programmer Mike Cariaso, Promethease is software that does gene-to-disease matching similar to that which 23andMe offered.

Cariaso's Promethease programming partner Greg Lennon says Promethease "is basically just a report consisting of the links between a given set of DNA variations and the literature about them. The basic Promethease program was — and remains — free for any individual to use."

But for $5, anyone with raw data from 23andMe can run that data through Promethease and get a report that would still tell them if, for example, they are at elevated risk for Alzheimer's. Not that this is advisable, but in an age when too many people turn to the internet for medical direction, it does happen.

In other words, the Pandora's box of direct-to-consumer genetic testing remains open. For now, anyway. Cariaso told *Genome* he hasn't heard from the FDA yet. "We're hoping to be left out of this kerfuffle," he says. "But we're probably open to making changes if requested."

Still, he doesn't agree with the FDA's contention that direct-to-consumer testing will cause customer concern and confusion. "Given a large enough sample, certainly somebody will overreact," Cariaso says. "The same is true of a bathroom scale or a thermometer. But I think there is a much greater opportunity for this information to do good than harm. No doctor is going to perform surgery based on a 23andMe report without follow-up testing."

And for Gholson Lyon, assistant professor in human genetics at Cold Spring Harbor Laboratory on Long Island, that's just the point. He agrees that genetic data on its own may not be a foolproof measure of the potential for us to develop certain diseases or a guarantee that we *won't* develop certain diseases. But the follow-up information, the doctor visits, the testing, and the building of a national or worldwide genetic database that could result, is worthwhile. "Information is power, and this information is helping people learn more about their health and leading them to talk with their physicians," he says. "Somehow the U.S. government finds it acceptable to store massive amounts of data about its own citizens and those of the rest of the world. But if the same people want to spend their own money to advance genomic medicine and possibly improve their own health in the process, they want to stop them."

For their part, FDA officials have said they support individuals' rights to access their own DNA data. "We just have concerns with how it's being interpreted," the FDA's Gutierrez recently told *Bloomberg Businessweek*.

And until 23andMe can prove that the science behind its interpretations is sound, you'll have to look elsewhere for information on what your genetic makeup might mean for your health. Whether or not that information is accurate and useful, for now, remains a matter of debate. ◦

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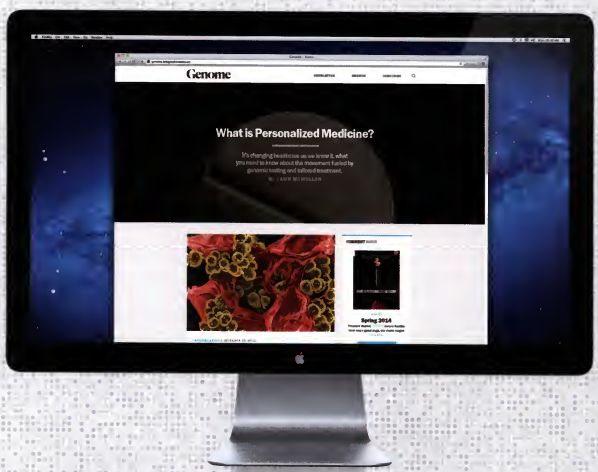

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HOW PERSONALIZED MEDICINE IS CHANGING: BREAST CANCER

Testing for dozens of biomarkers means oncologists can fine-tune breast cancer treatments in ways not even dreamed of just an eye-blink ago. **By Heather Millar**

ILLUSTRATION BY MARIO WAGNER

In 2011, a 52-year-old runner and yoga enthusiast walked into the office of Monica Loghin, a neuro-oncologist at MD Anderson Cancer Center in Houston, complaining of numbness and weakness in her lower limbs and difficulty controlling her bladder. ¶ The symptoms were of grave concern, as the patient had previously undergone surgery for breast cancer that had spread to her brain. If such a cancer returns post-surgery, that is often a sign the patient doesn't have much time left.

An MRI confirmed that the breast cancer had again spread to the woman's cerebrospinal fluid. Loghin ordered testing of that fluid to see if the patient might have certain biomarkers that could be targeted by existing drugs. (A biomarker is a DNA sequence or protein associated with the disease; different biomarkers can suggest specific treatments, depending on the disease and other factors.) She asked for tests that could detect tumor cells circulating in the blood.

The cancer cells in the fluid bathing the woman's spinal cord and brain chambers did, in fact, have a lot of the protein that controls a glucose (sugar) transporter that drives cancer cells. The cancer cells in the fluid also had a lot of HER2, a protein associated with aggressive breast cancers but also treatable with a drug called Herceptin (trastuzumab). The drug is usually taken intravenously, but Loghin had heard of a couple of cases in which Herceptin was delivered directly into the cerebrospinal fluid via a flexible tube, or catheter. The patient agreed to this experimental treatment.

It took only a week for the news to improve. After the first infusion of Herceptin, the patient's cancer numbers were down. Within a few weeks, her cancer cell numbers had fallen so low that her immune system had begun to take over, clearing out the remaining cancer cells. Nearly two and a half years later, the patient is still alive and well enough to do yoga. Another MD Anderson patient who had a similar disease profile and therapy is also alive and well one year after treatment.

This case outlines the dream of personalized medicine: A disease is analyzed at the molecular level. The analysis identifies a drug target. The drug gets delivered where it needs to go. The patient gets better. And while this hopeful scenario has yet to become commonplace, it is becoming more and more the norm for many breast cancer patients.

As it relates to breast cancer, such a targeted approach to treatment is increasingly possible. "I am optimistic about personalized medicine," Loghin says. "I want to develop a protocol to identify receptors in the spinal fluid and blood that we can use for targeted therapy."

Even more tailored treatment is on the horizon. In the next few years, patients with breast cancer can expect increasingly detailed diagnostic tests, tests that may predict side effects of treatments like chemotherapy or radiation, and better guidance in choosing the drug, or drugs, most likely to eradicate their disease. Genomic discoveries may also help patients with advanced, aggressive cancers, a group for whom even the latest treatments often fail. In these ways and many others, breast cancer prevention, treatment, and care are a microcosm of the slow but inevitable shift in healthcare.

EARLY PROGRESS

All cancers are caused by genetic mutations that somehow confer an advantage on the cancer cells, causing — or simply allowing — them to grow out of control. Genes, the biological "operating system" that determines how living things grow and maintain themselves, can get garbled in a variety of ways. As cells divide, genes may get miscopied. Or they can be copied too many times. Or perhaps a bit of genetic code gets left out. It turns out that different breast cancers might have very different profiles of these genetic mistakes, affecting different groups of genes.

Even before the human genome was completely sequenced in 2003, researchers had sketched in some of the biological details that would allow them to differentiate one breast cancer from another.

"In terms of a targeted approach to breast cancer, how far do you want to go back?" says J. Leonard Lichtenfeld, deputy chief medical officer for the American Cancer Society. "For example, we've been measuring hormone receptors for decades."

In 1951, researchers discovered that the hormone estrogen could drive the growth of breast cancer. Fifteen years later, they found the "receptor" for estrogen, the part of the cell that locks on to the hormone. That gave doctors a "target," something that medications could be designed to block. Similar discoveries were made for the hormone

progesterone. Nearly 75 percent of breast cancers are estrogen sensitive or progesterone sensitive or both, and drugs have been developed to interfere with the receptors for these hormones, thus slowing or stopping cancer growth or preventing a recurrence of the cancer.

In 1981, scientists identified a cancer-causing gene in mice. Four years later, they found the human version of this gene, HER2, the same gene that was overactive in the cerebrospinal fluid of the MD Anderson patient. Approximately 20 to 25 percent of breast tumors have this protein. A HER2-positive status used to mean a poor prognosis, but since the development of the genetically targeted drug Herceptin, patients with HER2-positive breast cancer actually benefit from some of the best treatment options.

While estrogen receptor, progesterone receptor, and HER2 tumor markers were helping target treatments in women diagnosed with cancer, progress was also being made identifying people at risk of developing cancer in the first place. In 1990, human geneticist Mary-Claire King showed that a location on chromosome 17 (subsequently identified by Myriad Genetics as BRCA1) was linked to many breast and ovarian cancers, proving wrong many who doubted the relationship between genetics and complex human diseases. Later in the 1990s, Myriad developed tests for BRCA1 and BRCA2, which both mark a susceptibility to breast cancer and ovarian cancer and tend to be hereditary.

But all of these advances — impressive and important as they were — simply identified single genes or proteins that might affect the course of a breast cancer case. The next breakthrough gave medical science a glimpse at our entire genetic blueprint, allowing for a global analysis and development of panels of genes for prognosis and targeted treatment of breast cancer.

THE AGE OF GENOMICS

Have you ever held some sand in your hand and assumed the grains were mostly the same? Then have you looked at that sand through a magnifying glass and gasped at the diversity of colors, shapes, and origins, the bits of glass, of shell, of stone, of bone, every hue of the rainbow? That's one way of understanding how our vision of breast cancer is changing thanks to genomics.

Once the entire human genome was sequenced in 2003, researchers and companies began to think about more complete genetic profiles of diseases like breast cancer. New prognostic tests soon followed. In 2006, researchers published pivotal results showing that the Oncotype DX test that measured estrogen-sensitive patients' risk of a breast cancer recurrence based on a panel of 21 "oncogenes," or genes that affect cancer cells, could also predict the degree of benefit a patient could expect from chemotherapy. In 2007, a 70-gene panel called MammaPrint won FDA approval. Both tests genetically analyzed a patient's tumor tissue, resulting in a score that predicted the risk of the cancer recurring. A low score meant the cancer probably wouldn't come back; a high score meant recurrence was likely. This allowed doctors to determine which patients might not need chemotherapy and which patients did.

"The good news is that breast cancer is one of the forms of cancer that has had a personalized approach for the longest time."

These developments that gave doctors tools to "stratify," or categorize, different cases of breast cancer are part of the oncology-ward argot. You can't sit in the waiting room of a care center without hearing snippets of conversation that include genetic and molecular information. "ER/PR status," "HER2 positive," "BRCA1 and BRCA2," Oncotype DX and MammaPrint scores — all these terms punctuate the patois of the breast cancer ward.

That's partly because genomics is poised to make treatment even

more hopeful for breast cancer patients as clinicians and researchers discern more genetic details that drive the disease — and that affect how patients respond to treatment. Doctors hope that better targeting will help patients whose disease has spread to other organs, or who relapse many years after the primary cancer — patients for whom there are now few options.

NEW INSIGHT, NEW DRUGS, NEW HOPE

It often surprises people to learn that a cancer's DNA is different from the DNA of the person who has the cancer. Often, the malignant DNA becomes wildly different. If it weren't a crazy genetic outlier, it probably wouldn't be cancer.

That reality led to the launch of The Cancer Genome Atlas (TCGA), a project of the National Cancer Institute that in 2009 brought together researchers from many disciplines to compile comprehensive genomic maps of 20 common cancers, including breast cancer. In the United Kingdom, the Breast Cancer Somatic Genetics study hopes to create genomic profiles of 500 breast cancer cases.

Just a decade ago, this kind of mapping would have involved a multistep process that cost millions and would have taken years or decades. Now, "next-generation" gene-sequencing technology has made it possible to analyze the genome of a breast cancer tumor with a one-step process for just thousands of dollars. This has accelerated our understanding of how breast cancers differ molecularly from one another.

"The most exciting thing that's happening now is the ability to do tumor sequencing," says Kelly Marcom, who started a hereditary breast cancer clinic at Duke University School of Medicine in the late 1990s. "It will be a while before we know what to do with all that information and how to marry that with the patient's own genetics and how to use that to refine treatment. But that's where the field is exploding."

"There's so much information at a raw data level," says Gavin Gordon, vice president at CollabRX, a San Francisco-based company that is trying to make the avalanche of genomic data understandable for doctors and patients. "Think of it this way: There used to be 50,000 academic papers on cancer annually. Now there are 100,000. There used to be just a few cancer drugs. Now there are about 500 in development."

Sequencing of tumor genomes has revealed several subtypes of breast cancer. In 2012, a paper published in the journal *Nature* reported results from the genomic sequencing of 510 breast tumors in 507 patients, part of the TCGA project. In all, the sequencing found 30,626 mutations in the cancer cells, which could be roughly divided into four groups:

- "Basal-like" tumors resemble the deepest layer of skin and account for a small, deadly percentage of cancers, often called "triple negative." These cancers appear to be entirely different from other breast cancers, actually sharing some features with a type of lung cancer and with ovarian cancer.
- Two related subtypes — "luminal A" and "luminal B" — include hormone-sensitive cancers. Doctors have struggled to understand why some of these cancers react to hormone-targeted drugs and others don't. Now doctors think that perhaps luminal A patients might do well with just hormone therapy while luminal B patients need more aggressive treatment such as chemotherapy.
- HER2-enriched cancers also turn out to fall into two groups, perhaps explaining why not all of these cancers react to the HER2-targeted drug Herceptin.

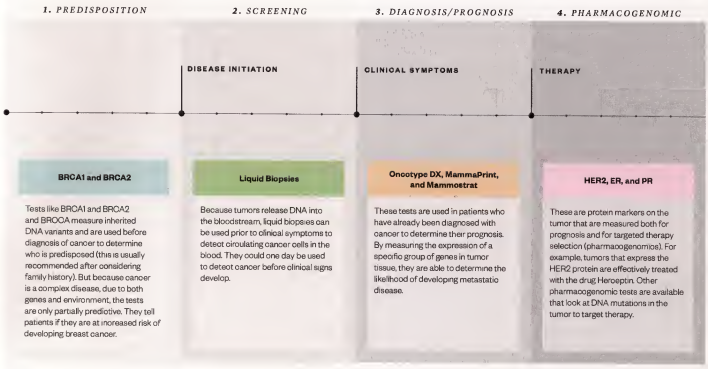
"There used to be just a few cancer drugs. Now there are about 500 in development."

"With the new tools, it's like a new microscope," explains University of North Carolina Medical School Professor Charles Perou, one of the *Nature* study authors and leader of the TCGA Breast Cancer Working Group. "Looking at the cancer DNA landscape, it's a 10,000-fold leap. We're learning a huge amount."

One of the biggest surprises, Perou says, is that molecular differences and biological pathways may connect cancers that we didn't even know were related. In other words, it's not where the cancer emerges

The Testing Timeline

At which point in the clinical course of a disease are various genomic tests used?



that may always be the most important. Rather, it's how the cancer cells work. That's why there is a movement toward reclassification of cancers based on their molecular profile versus traditional classification based on tissue of origin.

In addition to the connection that Perou's team found between basal-like breast tumors and some ovarian and lung tumors, other teams have found that certain breast cancers may share features with bladder cancer. A European team found that some breast cancers share regions of "hyper-mutations," overactive garbled DNA, with some types of lung and blood cancers.

The realization, thanks to genomic research, that where cancers start may not be as important as their molecular profile has helped researchers to think outside the box. Many new studies are exploring whether drugs thought useful for only one kind of cancer might work for cancers that arise in a variety of organs.

For instance, a November 2013 study combined Nexavar (sorafenib), currently approved to treat kidney and liver cancer, with Stivarga (regorafenib), approved for colorectal cancer, and a class of drugs called PI3K/AKT inhibitors. The researchers found this to be effective for a variety of cancers, including breast cancer.

Another study, presented at the 2013 Breast Cancer Symposium in San Antonio, showed that combining standard anti-hormone therapy Femara (letrozole) with Sprycel (dasatinib), a drug approved for chronic myeloid leukemia, doubled progression-free survival time in patients with advanced breast cancer. One of the ways that Sprycel works is by blocking a protein called Src. This protein has recently been implicated in the spread of breast cancer to bones.

In April 2013, the FDA awarded a similar combination — Femara plus an experimental Pfizer drug called palbociclib — "breakthrough therapy" status, meaning the drug's approval will be expedited. (The

combination met the primary goal of its phase 2 trial in February of this year.)

While there is still a lot of work to be done to translate this new knowledge into tests and treatments for patients, other studies have begun to pinpoint which genetic markers give clues as to which drugs might best fight a certain cancer. For instance, a January 2013 review by Perou and Washington University School of Medicine Professor Matthew Ellis summed up the results of six other genomics studies, which identified several genetic mutations that might make promising targets for new therapies.

"A new treatment paradigm is rapidly evolving," Perou and Ellis wrote in the review, published in *Cancer Discovery*. "Deep genomic analysis will drive treatment decisions based on ... cell type and pathway-matched therapies."

Every month, it seems, a team identifies a new possible target mutation. As breast cancer specialist and Stanford University Medical Center Professor George Sledge put it in a presentation at the Personalized Medicine World Conference in January, "It turns out that we don't need a magic bullet to cure cancer. We need a magic shotgun."

MORE TESTS, BETTER TESTS

Until the new discoveries lead to clinical research that makes truly personalized breast cancer medicine possible, the most immediate result of the genomic revolution has been the proliferation of new tests based on next-generation sequencing. Agendia, the company that pioneered MammaPrint, has now developed the Symphony Breast Cancer Genomic Profile to yield an even more detailed picture of each case. After the Supreme Court last year ruled that Myriad Genetics could not patent the BRCA1 and BRCA2 genes, the company announced that by 2015 it would replace its BRCAnalysis test with a broader myRisk panel that analyzes 25 genes associated with hereditary cancers, including breast, colorectal, ovarian, endometrial, pancreatic, prostate, gastric, and melanoma.

Several competing companies have started marketing BRCA tests, including Invitae, Ambry Genetics, and Quest Diagnostics, and the courts are likely to be busy for years with patent challenges and counterchallenges. At $1,500, Invitae's BRCA test is a less expensive alternative to Myriad's BRCAnalysis, and the company also offers a High-Risk Hereditary Breast Cancer panel that goes beyond BRCA testing and includes other genes associated with high-risk breast cancer syndromes. In addition to BRCA testing, Ambry Genetics offers BRCAplus and BreastNext, the latter of which looks at 16 genes implicated in hereditary breast cancer. And Quest's BRCAvantage tests for genetic risk of hereditary breast and ovarian cancer.

Beyond prognostic tests, women with early-stage cancer have other tools to gauge their risk of recurrence, like the recently FDA-approved Prosigna test from NanoString, an analysis of 50 genes. For patients with HER2 results that are unclear, the new TheraLink test may help clarify which drugs might be most effective. Another genomic test, called the RD-100i OSNA system, can detect even "micro-metastases" to a patient's lymph nodes, usually the first place that breast cancer spreads. A Washington University team is working to pinpoint patients who may test HER2 negative but nonetheless have an activating HER2 gene mutation that may affect their case.

Even more fine-grained tests are coming. A team at Purdue University is building on genomic information to flag cancers by how they process certain proteins. Other teams are working on genomic tests to identify "cell-free cancer DNA" — i.e., cancer DNA circulating in the bloodstream — as a way to monitor for remaining cancer cells that cannot be seen by conventional imaging methods, and to monitor response to treatment. These tests, which detect circulating tumor DNA, are often referred to as liquid biopsies. Janssen Diagnostics' CellSearch system is the only test of this kind so far to receive FDA clearance.

What all this means for patients now is that ever more information is becoming available to help guide decisions about treatment. Armed with genomic information, breast cancer patients may now feel comfortable forgoing certain treatments that might not be necessary for their unique case.

"We are at the beginning of a revolution," says the American Cancer Society's Lichtenfeld. "Breast cancer, as with many others — lung, melanoma, etc. — has a number of therapies in the pipeline, and that number is increasing dramatically. What does the future hold? Some successes, some failures. Will it lead to a cure? I can't say that. Will it lead to control of breast cancer? That's a real possibility."

BETTER CHOICES FOR PATIENTS

When a person is first diagnosed with cancer, the first panicked thoughts run along the lines of a medical sledgehammer: "Cut it out! Nuke it! Poison it!" Unfortunately, because cancers turn out to be so multifarious, "doing everything" doesn't always guarantee survival. Not only that, but aggressive treatments like chemotherapy and radiation may come with costs and side effects that can sometimes be as devastating as the original cancer.

Ann Meredith, a mother of two who lives outside Philadelphia, says she "completely flipped out" when she was diagnosed with breast cancer in August 2013. She says she was ready to try anything and consulted three doctors within a week, seriously considering chemotherapy, radiation, and a double mastectomy. The third doctor, Massimo

Cristofanilli at Jefferson University Hospital, suggested that Meredith have her tumor analyzed before she went the scorched-earth route.

Cristofanilli sent her biopsy sample to Agendia, which analyzed Meredith's tumor for hundreds of gene signatures. The results showed her cancer to be a luminal type: estrogen sensitive and low risk. Meredith opted for breast-conserving surgery, or lumpectomy, as well as radiation and hormone therapy.

"I really felt that because this information was available, it wasn't a cookie-cutter approach to cancer treatment," Meredith says. "It wasn't an emotional reaction to the fear. It was based on the best science available."

Obviously, this science will evolve. But some hopeful developments are likely to hit the clinic soon. Researchers are making gradual progress in understanding how best to treat aggressive and metastatic cancers. Genomic information is leading to new combination therapies for aggressive triple-negative and metastatic HER2 cancers. For example, one study showed a benefit to combining a traditional chemo drug, carboplatin, with a new DNA-damaging agent called a PARP inhibitor.

Oncologists have long known that combinations of drugs often work better than one drug alone. In a 2011 study, women with hormone-sensitive cancers (estrogen and/or progesterone positive) took a standard hormone-blocking drug, Aromasin (exemestane), in combination with Afinitor (everolimus), a drug that inhibits a protein called mTOR. This combination seemed to slow the progression of advanced cancers.

Recent research has focused on which drugs are best to partner with Herceptin, one of the first genomics-based drugs for breast cancer and one that targets a gene that directs the production of HER2.

At the annual San Antonio Breast Cancer Symposium last December, researchers reported that, after surgery, pairing Herceptin with the chemo drugs docetaxel and carboplatin appeared to be the best option. Another study presented at the symposium provided early evidence that combining Herceptin and Tykerb (lapatinib), another HER2-targeted drug, might work better than Herceptin alone. The researchers found that 84 percent of the patients who received this combination remained cancer free, compared to 76 percent who received Herceptin alone.

Another study found that for women with metastatic disease, giving Herceptin and an intravenous treatment called Perjeta (pertuzumab), which binds to a different part of the HER2 protein, slowed the progression of their cancer.

Others are working on genomic signatures that might help predict which patients will react badly to chemotherapy or radiation treatment. Inform Genomics has created a test to assess which patients are most at risk of nausea and vomiting and is developing a platform that will also assess the risk of four more common side effects: mouth sores, fatigue, difficulty thinking clearly, and nerve problems. A team at the University of Manchester in the United Kingdom is studying genomic signatures of long-term side effects of radiation treatment.

Many companies are finding genomic signatures to pair with particular drugs (aka "pharmacogenomics"). BioMarin in Northern California hopes to use genomics to predict which patients will benefit most from treatment with PARP inhibitors. Los Angeles-based Arno Therapeutics is working to understand which patients might benefit from drugs that block the activity of progesterone receptors. Teams at the University of Michigan and Sloan-Kettering Cancer Center are

"When I first heard I was hormone negative and HER2 positive, I thought, 'I'm dead.' But this treatment targeted my tumor type. In breast cancer, personalized medicine is moving quickly and slowly at the same time. In my case, I won the cancer lottery."

both working to find markers that might signal resistance to hormone therapy. As well, companies like Foundation Medicine and resources like My Cancer Genome are working to tie treatment to a deeper understanding of genomic changes that contribute to disease.

NEW SYSTEMS FOR TRIALS

While teams the world over are turning genomic discoveries into advances for patients, many researchers say the system for clinical trials needs to change. The current process tests potential treatments one at a time in "double-blind" trials, in which one group of patients gets the new therapy and a control group does not. Trials of new drugs go through three or four phases, checking first for safety, then whether it works or not, and finally tracking long-term effects. The process takes years.

But our growing understanding of cancer genomes is suggesting many, many possible new drug targets. We're also able to retest things that were rejected because they didn't work on enough people but might work if they were targeted to patients with the right genomic profile. Researchers say these probably need to be tested in combination, all at once, in a process that doesn't take decades. For instance, the NeoALTTO study, published in February 2012, showed that two anti-HER2 drugs in combination seem to work better than just one or the other.

The FDA is trying to adjust to these new realities by creating new procedures that allow drugs to be tested more quickly: Breakthrough Therapy is a new program announced in June 2013 that builds on previous programs such as Fast Track, Accelerated Approval, and Priority Review that might be used for therapies based on biomarkers.

Many companies and academics — Novartis, Amgen, and the Open Medicine Institute, to name just a few — are experimenting with new models for clinical trials. The one that is probably furthest along is the I-SPY trial of breast cancer patients conducted by the University of California at San Francisco and enrolling patients at medical centers around the country. In this study, researchers are testing multiple drugs from multiple companies all at once. In I-SPY, breast cancer patients agree to have systemic treatment before surgery, so that researchers can see how their tumors react. Depending on results, drugs can be added or dropped.

"The goal of the I-SPY trial is to quickly find the best drugs for each person and for us to really understand how to tailor treatment," explains Laura Esserman, principal investigator for the trial and director of the Carol Franc Buck Breast Care Center at UCSF.

The trial, which has completed phases 1 and 2, drops therapies that don't seem to work and "graduates" therapies that seem to have great benefit. This has already happened for drugs that seem to affect triple-negative or basal-like cancers and HER2 cancers. A third phase will begin this year.

Anne Marie Hallada, a 41-year-old mother of four from Palo Alto, California, felt a lump in her breast while nursing her youngest son, now 2. She enrolled in the I-SPY trial and started chemotherapy with a combination of Taxol (paclitaxel) and an experimental drug. After three weeks, the doctors took an MRI image of her breast to prepare for a biopsy. They couldn't find the tumor.

Arriving at the hospital for a chemo infusion the next day, Hallada met her oncologist in the hospital elevator. "She was jumping up and down, she was so excited by what had happened," Hallada says. Just to be safe, Hallada completed her chemo regimen and then had surgery. She opted not to have radiation but will have Herceptin infusions through this spring.

"In surgery, they just found a crater where the cancer had been," Hallada says. "When I first heard I was hormone negative and HER2 positive, I thought, 'I'm dead.' But this treatment targeted my tumor type. In breast cancer, personalized medicine is moving quickly and slowly at the same time. In my case, I won the cancer lottery."

WHAT'S NEXT?

Fifteen years ago, hormone receptors — those that made a patient estrogen or progesterone positive or negative — were the only real molecular targets for diagnosing and treating breast cancer in a personalized way. Now breast cancer patients can benefit from information on a variety of genomic markers: HER2, AKT1, PIK3CA, PTEN, and "kinase" genes that cause DNA to get rearranged or overexpressed in a way that leads to cancer. They can benefit from earlier and more detailed diagnosis and monitoring, thanks to genomic tests that build on our growing knowledge. But we're still in the very early days of truly personalized medicine, experts say.

The genes, gene interactions, and environmental factors that may drive or affect a case of breast cancer are dizzyingly complex. For instance, a study published in *Nature* in May 2012 analyzed the breast cancers of 100 patients. The researchers were able to identify "driver mutations" — that is, genetic changes that seemed to drive the cancer to grow — in about 40 different cancer genes. Some patients had only one driver mutation, but others had as many as six drivers. Neither pharmaceutical research nor genetic research nor federal regulation is set up to target six things at once. That means the disease will probably continue to surprise us for years or decades to come, researchers say.

Why do some cancers react to certain drugs and not to others? Why might a cancer become resistant to a drug? How can we predict these outcomes and changes? How do we choose a therapy that is just right for a particular patient? These are the kinds of questions researchers will try to answer in coming years.

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